```
=> fil reg; d ide 1-6
FILE 'REGISTRY' ENTERED AT 14:35:24 ON 15 JUL 2004
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   13 JUL 2004  HIGHEST RN 709042-93-3
DICTIONARY FILE UPDATES:  13 JUL 2004  HIGHEST RN 709042-93-3

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html


L10  ANSWER 1 OF 6  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   153559-76-3  REGISTRY
CN   3-Pyridinecarboxylic acid, 6-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-
     2-naphthalenyl)cyclopropyl]- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   AGN 192620
CN   ALRT 268
CN   CD 3127
CN   LG 100268
CN   LG 268
CN   LGD 100268
CN   LGD 1268
FS   3D CONCORD
DR   197730-94-2, 262615-35-0, 263723-53-1, 309956-42-1
MF   C24 H29 N O2
SR   CA
LC   STN Files:   ADISNEWS, AGRICOLA, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT,
       CHEMCATS, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, RTECS*,
       SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
DT.CA  CAplus document type:  Journal; Patent
RL.P   Roles from patents:  BIOL (Biological study); PREP (Preparation); PROC
       (Process); USES (Uses)
RLD.P  Roles for non-specific derivatives from patents:  BIOL (Biological
       study); USES (Uses)
RL.NP  Roles from non-patents:  BIOL (Biological study); PREP (Preparation);
       PROC (Process); USES (Uses)
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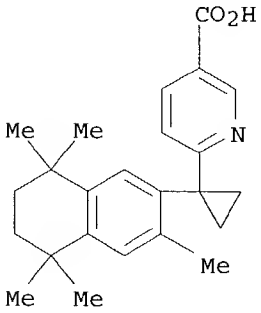
Note

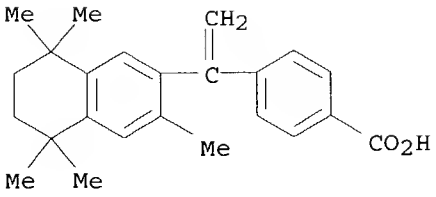
"RAR-specific retinoic acid" & "RXR-specific retinoic acid" are classes of compounds, not a specific compound, so there is no structure to display



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

96 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
96 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 2 OF 6 REGISTRY COPYRIGHT 2004 ACS on STN
RN 153559-49-0 REGISTRY
CN Benzoic acid, 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)ethenyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Bexarotene
CN LG 100069
CN LG 1069
CN LG 69
CN LG 69 (retinoid)
CN **LGD 1069**
CN RO 26-4455
CN Targret
CN Targretin
CN Targretyn
CN Targrexin
FS 3D CONCORD
MF C24 H28 O2
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, CIN, DIOGENES, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MRCK*, PHAR, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); MSC (Miscellaneous); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study)

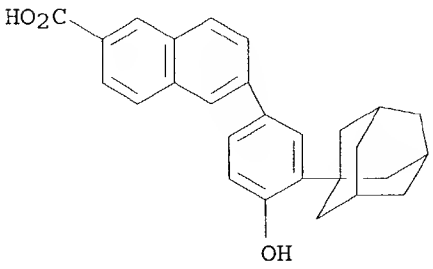


514/569

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

129 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
130 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2004 ACS on STN
RN 125316-60-1 REGISTRY
CN 2-Naphthalenecarboxylic acid, 6-(4-hydroxy-3-tricyclo[3.3.1.13,7]dec-1-ylphenyl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 6-[3-(1-Adamantyl)-4-hydroxyphenyl]-2-naphthalenecarboxylic acid
CN AHPN
CN **CD 437**
MF C27 H26 O3
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CA, CAPLUS, EMBASE, PHAR, PROUSDDR, RTECS*, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Conference; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PROC (Process); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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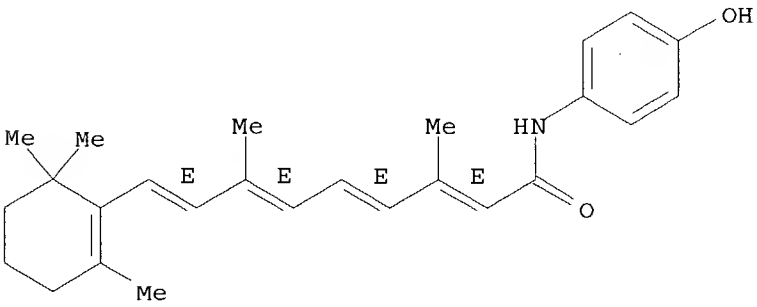
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
135 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2004 ACS on STN

RN 65646-68-6 REGISTRY
CN Retinamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (4-Hydroxyphenyl)retinamide
CN 4-HPR
CN all-trans-4'-Hydroxyretinanilide
CN all-trans-N-(4-Hydroxyphenyl)retinamide
CN **Fenretinide**
CN N-(4-Hydroxyphenyl)-all-trans-retinamide
CN N-(4-Hydroxyphenyl)retinamide
CN Retinoic acid p-hydroxyphenylamide
CN Ro 22-4667
FS STEREOSEARCH
MF C26 H33 N O2
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PROUSDDR, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: FORM (Formation, nonpreparative); PROC (Process); PRP (Properties)

Double bond geometry as shown.



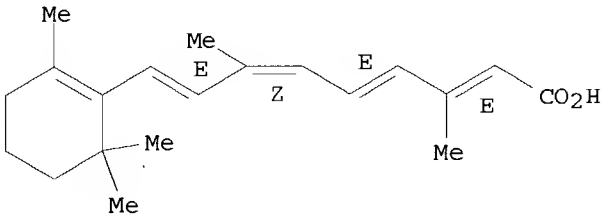
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

541 REFERENCES IN FILE CA (1907 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
543 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2004 ACS on STN
RN 5300-03-8 REGISTRY
CN Retinoic acid, 9-cis- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Retinoic acid, cis-9,trans-13- (8CI)
OTHER NAMES:
CN 9(Z)-Retinoic acid

CN **9-cis-Retinoic acid**
CN 9-cis-Tretinoin
CN AGN 192013
CN Alitretinoin
CN ALRT 1057
CN LG 100057
CN LGD 100057
CN LGD 1057
CN NSC 659772
CN Panretin
CN Panretyn
CN Panrexin
FS STEREOSEARCH
MF C20 H28 O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CIN, CSCHEM, DIOGENES, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PIRA, PROMT, PROUSDDR, PS, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties)

Double bond geometry as shown.



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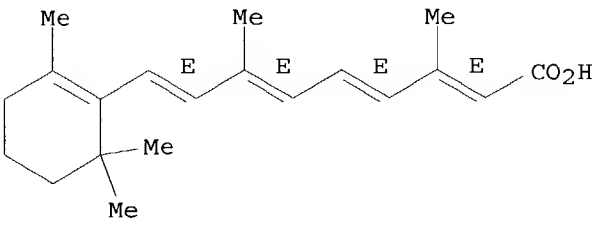
1252 REFERENCES IN FILE CA (1907 TO DATE)
19 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1259 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2004 ACS on STN
RN 302-79-4 REGISTRY
CN Retinoic acid (6CI, 9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Retinoic acid, all-trans- (8CI)
OTHER NAMES:
CN (all-E)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid

CN .beta.-Retinoic acid
CN 2,4,6,8-Nonatetraenoic acid, 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-, (all-E)-
CN 3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid
CN Aberel
CN AGN 100335
CN Airol
CN Aknoten
CN all-(E)-Retinoic acid
CN all-trans-.beta.-Retinoic acid
CN **all-trans-Retinoic acid**
CN all-trans-Tretinoin
CN all-trans-Vitamin A acid
CN ATRA
CN Atragen
CN Cordes Vas
CN Dermairol
CN Epi-Aberel
CN Eudyna
CN NSC 122578
CN NSC 122758
CN Renova
CN Retacnyl
CN Retin A
CN Ro 1-5488
CN trans-Retinoic acid
CN Tretin M
CN Tretin M, 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-, (all-E)-
CN Tretinoin
CN Vesanoid
CN Vesnaroid
CN Vitamin A acid
CN Vitamin A acid, all-trans-
CN Vitamin A1 acid, all-trans-
FS STEREOSEARCH
DR 7005-78-9, 56573-65-0, 187175-63-9
MF C20 H28 O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PIRA, PROMT, PROUSDDR, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses);

NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

12662 REFERENCES IN FILE CA (1907 TO DATE)
331 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
12685 REFERENCES IN FILE CAPLUS (1907 TO DATE)
23 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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=> fil reg; d ide l11
FILE 'REGISTRY' ENTERED AT 14:36:15 ON 15 JUL 2004
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   13 JUL 2004  HIGHEST RN 709042-93-3
DICTIONARY FILE UPDATES:  13 JUL 2004  HIGHEST RN 709042-93-3

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html


L11  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   218600-44-3  REGISTRY
CN   Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo- (9CI)  (CA INDEX
     NAME)
OTHER NAMES:
CN   CDDO
FS   STEREOSEARCH
MF   C31 H41 N O4
SR   CA
LC   STN Files:   CA, CAPLUS, CASREACT, IMSDRUGNEWS, IMSRESEARCH, TOXCENTER,
       USPAT2, USPATFULL
DT.CA  CAplus document type:  Dissertation; Journal; Patent
RL.P   Roles from patents:  BIOL (Biological study); PREP (Preparation); RACT
       (Reactant or reagent); USES (Uses)
RLD.P  Roles for non-specific derivatives from patents:  BIOL (Biological
       study); USES (Uses)
RL.NP  Roles from non-patents:  BIOL (Biological study); PREP (Preparation);
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Absolute stereochemistry.  Rotation (+).
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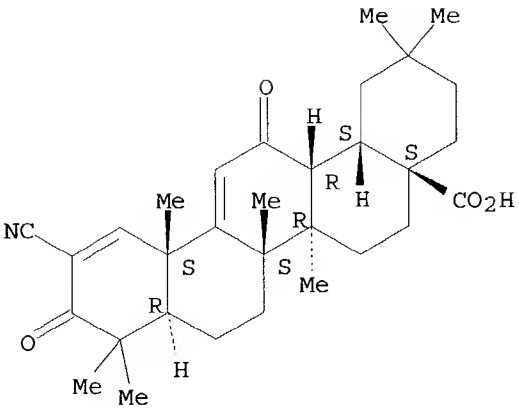


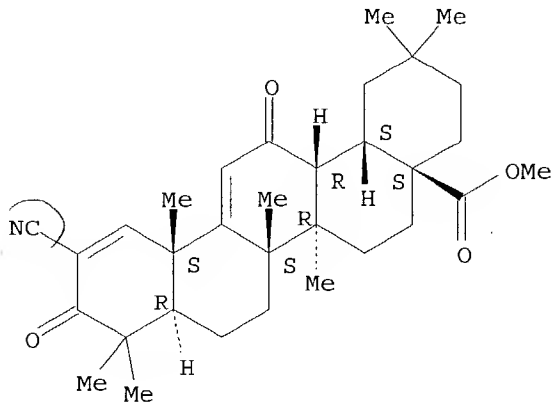
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

25 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
25 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> d ide l36

L36 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN **218600-53-4** REGISTRY
CN Oleana-1,9(11)-dien-28-oic acid, 2-cyano-3,12-dioxo-, methyl ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C32 H43 N O4
CI COM
SR CA
LC STN Files: CA, CAPLUS, CASREACT, IMSDRUGNEWS, IMSRESEARCH, PROUSDDR, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

Absolute stereochemistry. Rotation (+).



514/510

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

11 REFERENCES IN FILE CA (1907 TO DATE)
11 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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=> fil capl; d que l50; d que l51; d que l70; d que l73
FILE 'CAPLUS' ENTERED AT 16:05:18 ON 15 JUL 2004
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FILE COVERS 1907 - 15 Jul 2004  VOL 141 ISS 3
FILE LAST UPDATED: 14 Jul 2004  (20040714/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


L11           1 SEA FILE=REGISTRY ABB=ON  CDDO/CN
L36           1 SEA FILE=REGISTRY ABB=ON  218600-53-4
L37          56 SEA FILE=REGISTRY ABB=ON  (218600-44-3/BI OR 100629-51-4/BI OR
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                /BI OR 114-70-5/BI OR 125316-60-1/BI OR 13010-20-3/BI OR
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                65646-68-6/BI OR 671-16-9/BI OR 7689-03-4/BI OR 7722-84-1/BI
                OR 865-21-4/BI OR 92689-49-1/BI)
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L46      206898 SEA FILE=CAPLUS ABB=ON  L45
L47          26 SEA FILE=CAPLUS ABB=ON  L11 OR L36
L50          11 SEA FILE=CAPLUS ABB=ON  L47 AND L46



L11           1 SEA FILE=REGISTRY ABB=ON  CDDO/CN
L33       31728 SEA FILE=CAPLUS ABB=ON  DRUG INTERACTIONS+OLD,NT/CT
L34        2542 SEA FILE=CAPLUS ABB=ON  DRUG DELIVERY SYSTEMS+OLD/CT(L)COMB?/OB
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L36           1 SEA FILE=REGISTRY ABB=ON  218600-53-4
L47          26 SEA FILE=CAPLUS ABB=ON  L11 OR L36
L51           4 SEA FILE=CAPLUS ABB=ON  L47 AND (L33 OR L34)
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L23       26929 SEA FILE=CAPLUS ABB=ON  CHEMOTHERAP?/OBI
L25        4143 SEA FILE=CAPLUS ABB=ON  RETINOIDS/CT
L26      104210 SEA FILE=CAPLUS ABB=ON  T CELL#/OBI
L27       31894 SEA FILE=CAPLUS ABB=ON  IMMUNOSUPPRES?/OBI
L28       10949 SEA FILE=CAPLUS ABB=ON  IMMUNOMODULAT?/OBI
L29       39992 SEA FILE=CAPLUS ABB=ON  CORTICOSTEROID#/OBI
L30        1220 SEA FILE=CAPLUS ABB=ON  (TUMOR#(3A)RESECT?)/BI
L31       32938 SEA FILE=CAPLUS ABB=ON  CELL#/OBI(3A)(DEATH/OBI OR KILL?/OBI)
L32       30808 SEA FILE=CAPLUS ABB=ON  INHIBIT?/OBI(3A)GROWTH/OBI
L36           1 SEA FILE=REGISTRY ABB=ON  218600-53-4
L47          26 SEA FILE=CAPLUS ABB=ON  L11 OR L36
L70           2 SEA FILE=CAPLUS ABB=ON  L47 AND (L23 OR (L25 OR L26 OR L27 OR
                L28 OR L29 OR L30 OR L31 OR L32) OR L18)



L11           1 SEA FILE=REGISTRY ABB=ON  CDDO/CN
L17       38406 SEA FILE=CAPLUS ABB=ON  CELL DIFFERENTIATION/CT
L19       63099 SEA FILE=CAPLUS ABB=ON  APOPTOSIS/CT
L20      327876 SEA FILE=CAPLUS ABB=ON  NEOPLAS?/CW
L21      101114 SEA FILE=CAPLUS ABB=ON  ANTITUMOR AGENTS/CT
L22       11492 SEA FILE=CAPLUS ABB=ON  BCL2/OBI OR BCL 2/OBI
L24       38018 SEA FILE=CAPLUS ABB=ON  LEUKEMIA/CT
L36           1 SEA FILE=REGISTRY ABB=ON  218600-53-4
L47          26 SEA FILE=CAPLUS ABB=ON  L11 OR L36
L73          16 SEA FILE=CAPLUS ABB=ON  L47 AND ((L17 AND ((L19 OR L20 OR L21
                OR L22) OR L24)) OR (L19 AND (L21 OR L22 OR L24)) OR (L21 AND
                (L22 OR L24)) OR (L22 AND L24))


=> s l50 or l51 or l70 or l73

L114         18 L50 OR L51 OR L70 OR L73

=> fil uspatf; d que l76

FILE 'USPATFULL' ENTERED AT 16:05:19 ON 15 JUL 2004
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 15 Jul 2004 (20040715/PD)
FILE LAST UPDATED: 15 Jul 2004 (20040715/ED)
HIGHEST GRANTED PATENT NUMBER: US2004126357
HIGHEST APPLICATION PUBLICATION NUMBER: US2004139525
CA INDEXING IS CURRENT THROUGH 15 Jul 2004 (20040715/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 15 Jul 2004 (20040715/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2004

>>>  USPAT2 is now available.  USPATFULL contains full text of the     <<<
>>>  original, i.e., the earliest published granted patents or         <<<
>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent              <<<
>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention     <<<
>>>  are displayed in the PI (Patent Information) field of USPATFULL   <<<
>>>  records and may be searched in standard search fields, e.g., /PN, <<<
>>>  /PK, etc.                                                         <<<
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>>> enter this cluster. <<<
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>>> classifications, or claims, that may potentially change from <<<
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L11 1 SEA FILE=REGISTRY ABB=ON CDDO/CN
L36 1 SEA FILE=REGISTRY ABB=ON 218600-53-4
L76 5 SEA FILE=USPATFULL ABB=ON L11 OR L36

=> fil toxcenter; d que l77

FILE 'TOXCENTER' ENTERED AT 16:05:20 ON 15 JUL 2004
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FILE COVERS 1907 TO 13 Jul 2004 (20040713/ED)

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TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

L11 1 SEA FILE=REGISTRY ABB=ON CDDO/CN
L36 1 SEA FILE=REGISTRY ABB=ON 218600-53-4
L77 19 SEA FILE=TOXCENTER ABB=ON L11 OR L36

=> fil medl cancer; d que l107

FILE 'MEDLINE' ENTERED AT 16:05:20 ON 15 JUL 2004

FILE 'CANCERLIT' ENTERED AT 16:05:20 ON 15 JUL 2004

L105 39 SEA CDDO
L106 232457 SEA DRUG INTERACTIONS+NT/CT OR DRUG COMBINATIONS/CT OR DRUG THERAPY, COMBINATION/CT
L107 5 SEA L105 AND L106

=> fil embase; d que l110

FILE 'EMBASE' ENTERED AT 16:05:21 ON 15 JUL 2004
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FILE COVERS 1974 TO 9 Jul 2004 (20040709/ED)

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 EMBASE has been reloaded. Enter HELP RLOAD for details.

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 substance identification.


L108          22 SEA FILE=EMBASE ABB=ON  CDDO
L109      408001 SEA FILE=EMBASE ABB=ON  DRUG COMBINATION/CT OR DRUG INTERACTION
                 +NT/CT OR COMBINATION CHEMOTHERAPY/CT OR DRUG POTENTIATION/CT
L110           6 SEA FILE=EMBASE ABB=ON  L108 AND L109


=> fil drugu; d que l113

FILE 'DRUGU' ENTERED AT 16:05:22 ON 15 JUL 2004
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FILE LAST UPDATED: 15 JUL 2004        <20040715/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<

>>>  A RECENT REVIEW OF PSYCHIATRIC DISEASE KEYWORDS USED
     IN DERWENT DRUG FILE HAS PROMPTED A REVISION BASED
     ON STANDARD TERMS USED IN DSM-IV (DIAGNOSTIC AND
     STATISTICAL MANUAL OF MENTAL DISORDERS - FOURTH
     EDITION).
     FOR FURTHER DETAILS:
http://thomsonderwent.com/derwenthome/support/userguides/lit_guide



L111          56 SEA FILE=DRUGU ABB=ON  CDDO
L112      115135 SEA FILE=DRUGU ABB=ON  COMB./CT
L113           5 SEA FILE=DRUGU ABB=ON  L111 AND L112


=> fil BIOSIS, ADISCTI, DISSABS, CONFSCI, WPIDS;d que l101; d que l104

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FILE 'WPIDS' ENTERED AT 16:05:23 ON 15 JUL 2004
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L81           68 SEA CDDO
L91        66531 SEA CORTICOSTEROID# OR CORTICO STEROID#
L92        50932 SEA TACROLIMUS OR DOXORUBICIN# OR DECITABIN# OR DAUNORUBICIN#
                 OR DACTINOMYCIN# OR MITOXANTRON# OR CIPLASTIN#
L93        64590 SEA PROCARBAZIN# OR MITOMYCIN# OR CARBOPLATIN# OR BLEOMYCIN#
                 OR ETOPOSID# OR TENIPOSID# OR MECHLORETHAMIN#
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L101          16 SEA L81 AND (L91 OR L92 OR L93 OR L94 OR L95 OR L96 OR L97 OR
                 L98 OR L99)



L81           68 SEA CDDO
L82       152911 SEA CHEMOTHERAP?
L83      1630249 SEA CANCER? OR NEOPLAS? OR ANTINEOPLAS? OR TUMOR? OR TUMOUR?
                 OR ANTITUM?
L84       153415 SEA CYTOTOXI? OR CYTO(A) TOXI?
L104           6 SEA L81 AND L82 AND (L83 OR L84 OR L85 OR L86 OR L87 OR L88 OR
                 L89 OR L90)


=> s l101 or l104

L115         19 L101 OR L104

=> dup rem l114,l76,l107,l113,l110,l115,l77
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FILE 'DRUGU' ENTERED AT 16:06:11 ON 15 JUL 2004
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PROCESSING COMPLETED FOR L107
PROCESSING COMPLETED FOR L113
PROCESSING COMPLETED FOR L110
PROCESSING COMPLETED FOR L115
PROCESSING COMPLETED FOR L77
L116          49 DUP REM L114 L76 L107 L113 L110 L115 L77 (28 DUPLICATES REMOVED)
                 ANSWERS '1-18' FROM FILE CAPLUS
                 ANSWERS '19-23' FROM FILE USPATFULL
                 ANSWERS '24-25' FROM FILE MEDLINE
                 ANSWERS '26-30' FROM FILE DRUGU
                 ANSWERS '31-34' FROM FILE EMBASE
                 ANSWERS '35-46' FROM FILE BIOSIS
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ANSWER '47' FROM FILE DISSABS
ANSWERS '48-49' FROM FILE TOXCENTER

=> d ibib ed ab hitrn 1-23; d iall 24-49; fil hom

L116 ANSWER 1 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2004:218220 CAPLUS
DOCUMENT NUMBER: 140:350172
TITLE: Evidence Supporting a Role for Calcium in Apoptosis Induction by the Synthetic Triterpenoid 2-Cyano-3,12-dioxooleana-1,9-dien-28-oic Acid (CDDO)
AUTHOR(S): Hail, Numsen, Jr.; Konopleva, Marina; Sporn, Michael; Lotan, Reuben; Andreeff, Michael
CORPORATE SOURCE: Department of Thoracic/Head and Neck Medical Oncology, Section of Molecular Hematology and Therapy, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030-4095, USA
SOURCE: Journal of Biological Chemistry (2004), 279(12), 11179-11187
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 19 Mar 2004
AB The synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) is a novel anticancer agent that induces apoptosis in tumor cells. The cytotoxic stress underpinning CDDO-induced apoptosis has not been established. This study compared and contrasted the effects of CDDO on COLO 16 human skin cancer cells and their respiration-deficient (.rho.0) clones to elucidate the stress signal responsible for initiating apoptosis. CDDO promoted apoptosis in COLO 16 cells in a dose- and time-dependent manner. The .rho.0 clones appeared to be more sensitive to CDDO-induced apoptosis implying that the disruption of mitochondrial respiration was not directly assocd. with triggering cell death. After a 4-h exposure to CDDO, mitochondrial inner transmembrane potential-sensitive dyes revealed mitochondrial hyperpolarization in the COLO 16 cells and mitochondrial depolarization in the .rho.0 clones. Electron microscopy illustrated that this exposure also promoted mitochondrial condensation, endoplasmic reticulum dilation, and chromatin condensation in the COLO 16 cells. Endoplasmic reticulum dilation and chromatin condensation were also obsd. in the .rho.0 clones, but the mitochondria in these cells were markedly swollen implying that the disruption of intracellular Ca2+ homeostasis was assocd. with cell death. A Ca2+-sensitive dye confirmed that CDDO increased cytoplasmic free Ca2+ in the COLO 16 cells, their .rho.0 clones, as well as in malignant breast and lung epithelial cells. A cell-permeant Ca2+ chelator reduced the CDDO-induced increase in cytoplasmic free Ca2+, and inhibited caspase activation, the development of apoptotic morphol., and DNA fragmentation in the COLO 16 cells, implying that Ca2+ played a pivotal role in signaling the initiation of apoptosis.
IT **218600-44-3**, CDDO
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(role for calcium in apoptosis induction by the synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO))
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L116 ANSWER 2 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2004:71208 CAPLUS
DOCUMENT NUMBER: 141:17022

TITLE: Induction of redox imbalance and apoptosis in multiple myeloma cells by the novel triterpenoid 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid
AUTHOR(S): Ikeda, Takashi; Nakata, Yukiko; Kimura, Fumihiko; Sato, Ken; Anderson, Kenneth; Motoyoshi, Kazuo; Sporn, Michael; Kufe, Donald
CORPORATE SOURCE: Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA
SOURCE: Molecular Cancer Therapeutics (2004), 3(1), 39-45
CODEN: MCTOCF; ISSN: 1535-7163
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 29 Jan 2004
AB The synthetic oleanane triterpenoid 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO) and its chem. derivs. induce differentiation and apoptosis of human leukemia cells. The precise mechanisms responsible for the effects of CDDO, however, remain unclear. In the present study, we examd. the effects of CDDO and its C-28 imidazolide ester (CDDO-Im) on apoptosis of multiple myeloma (MM) cells. The results show that both CDDO and CDDO-Im are potent inducers of MM cell apoptosis and that CDDO-Im is more active than CDDO. CDDO-Im treatment was assocd. with (a) depletion of glutathione, (b) increases in reactive oxygen species, (c) a redn. of the Fas-assocd. death domain (FADD)-like interleukin-1-converting enzyme (FLICE) inhibitory protein, (d) activation of caspase-8, and (e) a decrease of the mitochondrial transmembrane potential. The reducing agents, N-acetyl-L-cysteine, DTT, and catalase inhibited each of these CDDO-Im-induced proapoptotic signals. Inhibition of caspase-8 with z-IETD-fmk also abrogated CDDO-Im-induced decreases of the mitochondrial transmembrane potential and inhibited apoptosis. These results demonstrate that CDDO-Im disrupts intracellular redox balance and thereby activates the extrinsic caspase-8-dependent apoptotic pathway. We further show that CDDO-Im induces apoptosis of primary MM cells at submicromolar concns. and that MM cells are more sensitive to this agent than normal bone marrow mononuclear cells. These results suggest that CDDO compds. have potential as new agents for the treatment of MM.
IT **179241-78-2**, Caspase-8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(induction of redox imbalance and apoptosis in multiple myeloma cells by the novel triterpenoid 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid)
IT **218600-44-3**, CDDO
RL: DMA (Drug mechanism of action); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(induction of redox imbalance and apoptosis in multiple myeloma cells by the novel triterpenoid 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid)
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L116 ANSWER 3 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 2003:780118 CAPLUS
DOCUMENT NUMBER: 140:174590
TITLE: Activation of Peroxisome Proliferator-activated Receptor .gamma. by a Novel Synthetic Triterpenoid 2-Cyano-3,12-dioxooleana-1,9-dien-28-oic Acid Induces Growth Arrest and Apoptosis in Breast Cancer Cells
AUTHOR(S): Lapillonne, Helene; Konopleva, Marina; Tsao, Twee; Gold, David; McQueen, Teresa; Sutherland, Robert L.; Madden, Timothy; Andreeff, Michael
CORPORATE SOURCE: Department of Blood and Marrow Transplantation, Section of Molecular hematology and Therapy, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030-4009, USA

SOURCE: Cancer Research (2003), 63(18), 5926-5939
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 06 Oct 2003
AB Peroxisome proliferator-activated receptor .gamma. (PPAR.gamma.) is a member of the nuclear hormonal receptor superfamily expressed in a large no. of human cancers. Here, we demonstrate that PPAR.gamma. is expressed and transcriptionally active in breast cancer cells independent of their p53, estrogen receptor, or human epidermal growth factor receptor 2 status. 2-Cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO), a novel synthetic triterpenoid, is a ligand for PPAR. We investigated the mol. mechanisms of CDDO on proliferation and apoptosis in breast cancer cells. In all breast cancer cell lines studied, CDDO transactivated PPAR.gamma., induced dose- and time-dependent cell growth inhibition, cell cycle arrest in G1-S and G2-M, and apoptosis. We then used differential cDNA array anal. to investigate the mol. changes induced by CDDO. After 16-h exposure of MCF-7 and MDA-MB-435 cells to CDDO, we found genes encoding the following proteins to be up-regulated in both cell lines: p21Waf1/CIP1; GADD153; CAAT/enhancer binding protein transcription factor family members; and proteins involved in the ubiquitin-proteasome pathway. Among the down-regulated genes, we focused on the genes encoding cyclin D1, proliferating cell nuclear antigen, and the insulin receptor substrate 1. Using Western blot anal. and/or real-time PCR, we confirmed that CDDO regulated the expression of cyclin D1, p21Waf1/CIP1, and Bcl-2. Cyclin D1 and p21Waf1/CIP1 were addnl. confirmed as important mediators of CDDO growth inhibition in genetically modified breast cancer cell lines. CDDO was able to significantly reduce the growth of MDA-MB-435 tumor cells in immunodeficient mice in vivo. The finding that CDDO can target genes crit. for the regulation of cell cycle, apoptosis, and breast carcinogenesis suggests usage of CDDO as novel targeted therapy in breast cancer.
IT **218600-44-3**, CDDO
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(triterpenoid cyanodioxooleanadienoate induces apoptosis and growth arrest via PPARgamma receptor)
REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L116 ANSWER 4 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 2003:733807 CAPLUS
DOCUMENT NUMBER: 140:174581
TITLE: The Novel Triterpenoid CDDO and its Derivatives Induce Apoptosis by Disruption of Intracellular Redox Balance
AUTHOR(S): Ikeda, Takashi; Sporn, Michael; Honda, Tadashi; Gribble, Gordon W.; Kufe, Donald
CORPORATE SOURCE: Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Cancer Research (2003), 63(17), 5551-5558
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 19 Sep 2003
AB The novel oleanane triterpenoid 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO) induces apoptosis of human leukemia cells by activation of the extrinsic caspase-8 pathway. The mechanisms responsible for the proapoptotic effects of CDDO are unknown. The present studies demonstrate that CDDO activates the c-Jun NH2-terminal kinase and p38 mitogen-activated protein kinase in U-937 leukemia cells. The results

also show that CDDO activates stress kinases by increasing levels of reactive oxygen species and decreasing intracellular glutathione (GSH) concns. Similar findings were obtained with the C-28 Me ester (CDDO-Me) and C-28 imidazolide ester (CDDO-Im) derivs. The results also demonstrate that CDDO-induced: (a) stimulation of Jun NH2-terminal kinase; (b) activation of caspase-8; (c) loss of mitochondrial transmembrane potential; (d) release of cytochrome c; and (e) cleavage of caspase-3 are blocked by pretreatment with the antioxidant N-acetyl-L-cysteine and GSH but not with cysteine. In concert with these results, CDDO-induced apoptosis is also abrogated by N-acetyl-L-cysteine and GSH. These findings demonstrate that CDDO and its derivs. disrupt intracellular redox balance and thereby induce apoptosis.

IT **169592-56-7**, Caspase-3
RL: BSU (Biological study, unclassified); BIOL (Biological study) (activation; novel triterpenoid CDDO and its derivs. induce apoptosis by disruption of intracellular redox balance)

IT **218600-53-4**
RL: DMA (Drug mechanism of action); BIOL (Biological study) (novel triterpenoid CDDO and its derivs. induce apoptosis by disruption of intracellular redox balance)

IT **179241-78-2**, Caspase-8
RL: BSU (Biological study, unclassified); BIOL (Biological study) (novel triterpenoid CDDO and its derivs. induce apoptosis in myeloid leukemia cells by disruption of intracellular redox balance)

IT **218600-44-3**, CDDO
RL: DMA (Drug mechanism of action); BIOL (Biological study) (novel triterpenoid CDDO and its derivs. induce apoptosis in myeloid leukemia cells by disruption of intracellular redox balance)

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L116 ANSWER 5 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 2003:832882 CAPLUS
DOCUMENT NUMBER: 140:399426
TITLE: Synthetic triterpenoids activate a pathway for apoptosis in AML cells involving downregulation of FLIP and sensitization to TRAIL
AUTHOR(S): Suh, W.-S.; Kim, Y. S.; Schimmer, A. D.; Kitada, S.; Minden, M.; Andreeff, M.; Suh, N.; Sporn, M.; Reed, J. C.
CORPORATE SOURCE: The Burnham Institute, La Jolla, CA, 92037, USA
SOURCE: Leukemia (2003), 17(11), 2122-2129
CODEN: LEUKED; ISSN: 0887-6924
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 24 Oct 2003
AB Acute myelogenous leukemia (AML) remains a deadly disease for most adult patients, due primarily to the emergence of chemoresistant cells. Defects in apoptosis pathways make important contributions to chemoresistance, suggesting a need to restore apoptosis sensitivity or to identify alternative pathways for apoptosis induction. Triterpenoids represent a class of naturally occurring and synthetic compds. with demonstrated antitumor activity, including 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO) and its Me ester (CDDO-m). We explored the effects of CDDO and CDDO-m in vitro on established AML cell lines (HL-60, U937, AML-2) and on freshly isolated AML blasts. CDDO and CDDO-m reduced the viability of all AML cell lines tested in a dose-dependent manner, with EDs for killing 50% of cells (ED50) within 48 h of .apprx.1 and 0.5 .mu.M, resp. CDDO or CDDO-m also induced substantial increases in cell death in five out of 10 samples of primary AML blasts. Cell death induced by CDDO and CDDO-m was attributed to apoptosis, based on characteristic cell morphol. and

evidence of caspase activation. Immunoblot anal. demonstrated proteolytic processing of caspase-3, -7, and -8, but not caspase-9, suggesting the involvement of the extrinsic' pathway, linked to apoptosis induction by TNF-family death receptors. Accordingly, CDDO and CDDO-m induced concn.-dependent redns. in the levels of FLIP protein, an endogenous antagonist of caspase-8, without altering the levels of several other apoptosis-relevant proteins. Redns. in FLIP were rapid, detectable within 3 h after exposure of AML cell lines to CDDO or CDDO-m. CDDO and CDDO-m also sensitized two of four leukemia lines to TRAIL, a TNF-family death ligand. The findings suggest that synthetic triterpenoids warrant further investigation in the treatment of AML, alone or in combination with TRAIL or other immune-based therapies.

IT **169592-56-7**, Caspase-3 **179241-78-2**, Caspase-8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(synthetic triterpenoids activate a pathway for apoptosis in AML cells involving downregulation of FLIP and sensitization to TRAIL)

IT **218600-44-3 218600-53-4**
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthetic triterpenoids activate a pathway for apoptosis in AML cells involving downregulation of FLIP and sensitization to TRAIL)

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L116 ANSWER 6 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 2003:220384 CAPLUS
DOCUMENT NUMBER: 139:173329
TITLE: Synthetic Triterpenoids Enhance Transforming Growth Factor .beta./Smad Signaling
AUTHOR(S): Suh, Nanjoo; Roberts, Anita B.; Birkey Reffey, Stephanie; Miyazono, Kohei; Itoh, Susumu; ten Dijke, Peter; Heiss, Elke H.; Place, Andrew E.; Risingsong, Renee; Williams, Charlotte R.; Honda, Tadashi; Gribble, Gordon W.; Sporn, Michael B.
CORPORATE SOURCE: Dartmouth Medical School and Dartmouth College, Hanover, NH, 03755, USA
SOURCE: Cancer Research (2003), 63(6), 1371-1376
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 21 Mar 2003
AB We have studied the effects of two new synthetic triterpenoids, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) and its deriv., 1-(2-cyano-3,12-dioxooleana-1,9-dien-28-oyl) imidazole (CDDO-Im), on transforming growth factor (TGF)-.beta./Smad signaling. These agents, at nanomolar concns., increase the expression of TGF-.beta.-dependent genes, such as those for plasminogen activator inhibitor 1 and the type II TGF-.beta. receptor, and they synergize with TGF-.beta. in this regard. They prolong the activation of Smad2 induced by TGF-.beta. and markedly enhance the ability of Smad3 to activate a Smad binding element, CAGA-luciferase. In transfection assays, they reverse the inhibitory effects of Smad7. CDDO and CDDO-Im also enhance Smad signaling in the pathways of two other members of the TGF-.beta. superfamily, namely, activin and bone morphogenetic protein. Finally, these triterpenoids induce expression of the transcriptional coactivator p300-CBP-assocd. factor and synergize with TGF-.beta. in this regard. These are the first studies to report enhancement of Smad signaling by synthetic triterpenoids and should further their optimal use for applications in prevention or treatment of diseases in which there is aberrant function of TGF-.beta..

IT **218600-44-3**, CDDO
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)
(synthetic triterpenoids enhance TGF-.beta./Smad signaling)
REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L116 ANSWER 7 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 2002:465747 CAPLUS
DOCUMENT NUMBER: 137:41724
TITLE: CDDO (2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid) compounds and combinations with other **chemotherapeutics** for the treatment of cancer and graft vs. host disease
INVENTOR(S): Konopleva, Marina; Andreef, Michael; Sporn, Michael
PATENT ASSIGNEE(S): Board of Regents, the University of Texas System, USA
SOURCE: PCT Int. Appl., 184 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002047611	A2	20020620	WO 2001-US44541	20011128
WO 2002047611	C1	20030626		
WO 2002047611	A3	20031224		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002043246	A5	20020624	AU 2002-43246	20011128
US 2003119732	A1	20030626	US 2001-998009	20011128
EP 1395255	A2	20040310	EP 2001-989130	20011128
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-253673P P 20001128
WO 2001-US44541 W 20011128

ED Entered STN: 21 Jun 2002
AB CDDO compds. in combination with other chemotherapeutic agents induce and potentiate cytotoxicity and apoptosis in cancer cells. One class of chemotherapeutic agents include retinoids. Cancer therapies based on these combination therapies are provided. Also provided are methods to treat graft vs. host diseases using the CDDO compds.
IT **218600-44-3** **218600-53-4**
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CDDO compds. and combinations with other **chemotherapeutics** for treatment of cancer and graft vs. host disease)
IT **169592-56-7**, Caspase 3 **179241-78-2**, Caspase 8
201556-11-8, Procaspase 3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CDDO compds. and combinations with other **chemotherapeutics** for treatment of cancer and graft vs. host disease)
IT **50-18-0**, Cyclophosphamide **50-76-0**, Dactinomycin
51-21-8, 5-Fluorouracil **51-75-2**, Mechlorethamine
52-24-4, Thiotepa **55-98-1**, Busulfan **57-22-7**,
Vincristine **59-05-2**, Methotrexate **114-70-5**, Sodium

phenylacetate **147-94-4**, Ara-C **148-82-3**, Melphalan **154-93-8**, Carmustine **156-54-7**, Sodium butyrate **302-79-4**, all-trans-Retinoic acid **305-03-3**, Chlorambucil **645-05-6**, Hexamethylmelamine **671-16-9**, Procarbazine **865-21-4**, Vinblastine **1404-00-8**, Mitomycin **2353-33-5**, Decitabine **3778-73-2**, Ifosfamide **4342-03-4**, Dacarbazine **5300-03-8**, 9-cis-Retinoic acid **7689-03-4**, Camptothecin **7722-84-1**, Hydrogen peroxide, biological studies **10540-29-1**, Tamoxifen **11056-06-7**, Bleomycin **13010-20-3**, Nitrosurea **13010-47-4**, Lomustine **13909-09-6**, Semustine **14913-33-8**, Transplatin **15663-27-1**, Cisplatin **18378-89-7**, Plicamycin **18883-66-4**, Streptozocin **20830-81-3**, Daunorubicin **23214-92-8**, Doxorubicin **25316-40-9**, Adriamycin **29767-20-2**, Teniposide **33069-62-4**, Taxol **33419-42-0**, Etoposide **41575-94-4**, Carboplatin **65271-80-9**, Mitoxantrone **65646-68-6**, Fenretinide **92689-49-1**, Annamycin **100629-51-4**, Bryostatin **104987-11-3**, Tacrolimus **110417-88-4**, Dolastatin 10 **125316-60-1**, CD437 **153559-49-0**, LGD1069 **153559-76-3**, LG100268 **218600-44-3D**, derivs. **220578-59-6**, Mylotarg
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CDDO compds. and combinations with other **chemotherapeutics** for treatment of cancer and graft vs. host disease)

L116 ANSWER 8 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 11
ACCESSION NUMBER: 2002:505732 CAPLUS
DOCUMENT NUMBER: 138:66283
TITLE: An inducible pathway for degradation of FLIP protein sensitizes tumor cells to TRAIL-induced apoptosis
AUTHOR(S): Kim, Youngsoo; Suh, Nanjoo; Sporn, Michael; Reed, John C.
CORPORATE SOURCE: Burnham Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of Biological Chemistry (2002), 277(25), 22320-22329
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 07 Jul 2002
AB TRAIL (Apo2 ligand) is a member of the tumor necrosis factor (TNF) family of cytokines that induces apoptosis. Because TRAIL preferentially kills tumor cells, sparing normal tissues, interest has emerged in applying this biol. factor for cancer therapy in humans. However, not all tumors respond to TRAIL, raising questions about resistance mechanisms. We demonstrate here that a variety of natural and synthetic ligands of peroxisome proliferator-activated receptor-.gamma. (PPAR.gamma.) sensitize tumor but not normal cells to apoptosis induction by TRAIL. PPAR.gamma. ligands selectively reduce levels of FLIP, an apoptosis-suppressing protein that blocks early events in TRAIL/TNF family death receptor signaling. Both PPAR.gamma. agonists and antagonists displayed these effects, regardless of the levels of PPAR.gamma. expression and even in the presence of a PPAR.gamma. dominant-neg. mutant, indicating a PPAR.gamma.-independent mechanism. Redns. in FLIP and sensitization to TRAIL-induced apoptosis were also not correlated with NF-.kappa.B, further suggesting a novel mechanism. PPAR.gamma. modulators induced ubiquitination and proteasome-dependent degrdn. of FLIP, without concomitant redns. in FLIP mRNA. The findings suggest the existence of a pharmacol. regulated novel target of this class of drugs that controls

FLIP protein turnover, and raise the possibility of combining PPAR.gamma. modulators with TRAIL for more efficacious elimination of tumor cells through apoptosis.

IT **218600-44-3**, CDDO **218600-53-4**
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); BIOL (Biological study); USES (Uses)
(inducible pathway for degrdn. of FLIP protein sensitizes tumor cells to TRAIL-induced apoptosis)

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L116 ANSWER 9 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 12

ACCESSION NUMBER: 2002:371217 CAPLUS
DOCUMENT NUMBER: 137:304401
TITLE: The novel triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) potently enhances apoptosis induced by tumor necrosis factor in human leukemia cells
AUTHOR(S): Stadheim, Terrance A.; Suh, Nanjoo; Ganju, Neema; Sporn, Michael B.; Eastman, Alan
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, NH, 03755, USA
SOURCE: Journal of Biological Chemistry (2002), 277(19), 16448-16455
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 19 May 2002

AB Tumor necrosis factor (TNF) is a potent activator of the nuclear factor-.kappa.B (NF-.kappa.B) pathway that leads to upregulation of antiapoptotic proteins. Hence, TNF induces apoptosis in the presence of inhibitors of protein or RNA synthesis. This work reports that the title triterpenoid (CDDO) inhibits NF-.kappa.B-mediated gene expression at a step after translocation of activated NF-.kappa.B to the nucleus. This effect appears specific for the NF-.kappa.B pathway as CDDO did not inhibit gene expression induced by the phorbol ester 12-O-tetradecanoylphorbol-13-acetate. CDDO in combination with TNF caused a dramatic increase in apoptosis in ML-1 leukemia cells that was assocd. with activation of caspase-8, cleavage of Bid, translocation of Bax, cytochrome c release, and caspase-3 activation. Expts. with caspase inhibitors demonstrated that caspase-8 was an initiator of this pathway. TNF also induced a transient activation of c-Jun N-terminal kinase (JNK), which upon addn. of CDDO was converted to a sustained activation. The activation of JNK was also dependent on caspase-8. Sustained activation of JNK is frequently proapoptotic, yet inhibition of JNK did not prevent Bax translocation or cytochrome c release, demonstrating its lack of involvement in CDDO/TNF-induced apoptosis. Apoptosis was acutely induced by CDDO/TNF in every leukemia cell line tested, including those that overexpress Bcl-xL, suggesting that the mitochondrial pathway is not required for apoptosis by this combination. These results suggest that the apoptotic potency of the CDDO/TNF combination occurs through selective inhibition of NF-.kappa.B-dependent antiapoptotic proteins, bypassing potential mitochondrial resistance mechanisms; this may provide a basis for the development of novel approaches to the treatment of leukemia.

IT **218600-44-3**, CDDO
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid enhancement of apoptosis induced by tumor necrosis factor in human leukemia cells)

IT **169592-56-7**, Caspase 3 **179241-78-2**, Caspase 8

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid enhancement of apoptosis induced by tumor necrosis factor in human leukemia cells in relation to activation of)
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L116 ANSWER 10 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 13
ACCESSION NUMBER: 2002:805259 CAPLUS
DOCUMENT NUMBER: 138:314077
TITLE: The triterpenoid CDDO induces apoptosis in refractory CLL B cells
AUTHOR(S): Pedersen, Irene M.; Kitada, Shinichi; Schimmer, Aaron; Kim, Youngsoo; Zapata, Juan M.; Charboneau, Lula; Rassenti, Laura; Andreeff, Michael; Bennett, Frank; Sporn, Michael B.; Liotta, Lance D.; Kipps, Thomas J.; Reed, John C.
CORPORATE SOURCE: The Burnham Institute and University of California-San Diego, La Jolla, CA, USA
SOURCE: Blood (2002), 100(8), 2965-2972
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 23 Oct 2002
AB Chronic lymphocytic leukemia (CLL) cells develop chemo-resistance over time. Most anticancer agents function through induction of apoptosis, and therefore resistance against these agents is likely to be caused by selection for CLL cells with defects in the particular apoptosis pathway that is triggered by these drugs. Anticancer agents that function through alternative apoptotic pathways might therefore be useful in treating chemo-resistant CLL. Triterpenoids represent a class of naturally occurring and synthetic compds. with demonstrated antitumor activity. We examd. the effects of CDDO (triterpenoid 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid) on CLL B cells in vitro. CDDO induced apoptosis in a dose-dependent manner in all (n = 30) CLL samples tested, including previously untreated and chemo-resistant CLL specimens. CDDO induced rapid proteolytic processing of caspase-8, but not caspase-9, in CLL B cells, suggesting activation of a mitochondria-independent pathway. CDDO-induced apoptosis of CLL B cells was blocked by cytokine response modifier A (CrmA), a suppressor of caspase-8, but not by X-linked inhibitor of apoptosis protein-baculovirus IAP repeat-3 (XIAP-BIR3), a fragment of XIAP, which selectively inhibits caspase-9. Examn. of CDDO effects on expression of several apoptosis-relevant genes demonstrated significant redns. in the levels of caspase-8 homolog Fas-ligand interleukin-1-converting enzyme (FLICE)-inhibitory protein (c-FLIP), an endogenous antagonist of caspase-8. However, redns. of FLIP achieved by FLIP antisense oligonucleotides were insufficient for triggering apoptosis, indicating that CDDO has other targets in CLL B cells besides FLIP. These data suggest that the synthetic triterpenoid CDDO should be further explored as a possible therapeutic agent for treatment of chemo-resistant CLL.
IT **179241-78-2**, Caspase-8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(triterpenoid CDDO (2-cyano-3, 12-dioxoolean-1,9-dien-28-oic acid) induces apoptosis in refractory chronic lymphocytic leukemia B cells)
IT **218600-44-3**, CDDO
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(triterpenoid CDDO (2-cyano-3, 12-dioxoolean-1,9-dien-28-oic acid) induces apoptosis in refractory chronic lymphocytic leukemia B cells)
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L116 ANSWER 11 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 14
ACCESSION NUMBER: 2002:29939 CAPLUS
DOCUMENT NUMBER: 136:318974
TITLE: Novel triterpenoid CDDO-Me is a potent inducer of apoptosis and differentiation in acute myelogenous leukemia
AUTHOR(S): Konopleva, Marina; Tsao, Twee; Ruvolo, Peter; Stiouf, Irina; Estrov, Zeev; Leysath, Clinton E.; Zhao, Shourong; Harris, David; Chang, Shirong; Jackson, C. Ellen; Munsell, Mark; Suh, Nanjoo; Gribble, Gordon; Honda, Tadashi; May, W. Stratford; Sporn, Michael B.; Andreeff, Michael
CORPORATE SOURCE: Department of Blood and Marrow Transplantation, Section of Molecular Hematology and Therapy, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Blood (2002), 99(1), 326-335
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 11 Jan 2002
AB The synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oleic acid (CDDO) inhibits proliferation and induces differentiation and apoptosis in myeloid leukemia cells. This work studied the effects of the C-28 Me ester of CDDO, CDDO-Me, on cell growth and apoptosis of leukemic cell lines and primary acute myelogenous leukemia (AML). CDDO-Me decreased the viability of leukemic cell lines, including multidrug resistant (MDR)-1-overexpressing, p53null HL-60-Dox and primary AML cells, and it was 3-5-fold more active than CDDO. CDDO-Me induced a loss of mitochondrial membrane potential, induced caspase-3 cleavage, and increased annexin V binding and DNA fragmentation, suggesting the induction of apoptosis. CDDO-Me induced the proapoptotic Bax protein that precedes caspase activation. Furthermore, CDDO-Me inhibited the activation of ERK1/2, as detd. by the inhibition of mitochondrial ERK1/2 phosphorylation, and it blocked Bcl-2 phosphorylation, rendering Bcl-2 less antiapoptotic. CDDO-Me induced granulo-monocytic differentiation in HL-60 cells and monocytic differentiation in primary cells. Colony formation of AML progenitors was inhibited in a concn.-dependent fashion, whereas normal CD34+ progenitor cells were less affected. Combinations with all-trans-retinoic acid or the retinoic acid receptor-specific ligand LG100268 enhanced the effects of CDDO-Me on the cell viability and terminal differentiation of myeloid leukemic cell lines. In conclusion, CDDO-Me is an MDR-1- and a p53-independent compd. that exerts strong antiproliferative, apoptotic, and differentiating effects in myeloid leukemic cell lines and in primary AML samples when used in submicromolar concns. The differential effects of CDDO-Me on leukemic and normal progenitor cells suggest that CDDO-Me has potential as a novel compd. in the treatment of hematol. malignancies.
IT **218600-44-3**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(triterpenoid CDDO vs. its ester CDDO-Me induction of apoptosis and differentiation in acute myelogenous leukemia)
IT **218600-53-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(triterpenoid CDDO-Me induction of apoptosis and differentiation in acute myelogenous leukemia)
IT **169592-56-7**, Caspase 3

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(triterpenoid CDDO-Me induction of apoptosis and differentiation in acute myelogenous leukemia in relation to effects on)

IT **302-79-4**, all-trans-Retinoic acid **153559-76-3**, LG 100268
RL: PAC (Pharmacological activity); BIOL (Biological study)
(triterpenoid CDDO-Me induction of apoptosis and differentiation in acute myelogenous leukemia response to)

REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L116 ANSWER 12 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 15
ACCESSION NUMBER: 2002:95270 CAPLUS
DOCUMENT NUMBER: 136:379616
TITLE: Identification of a novel synthetic triterpenoid, methyl-2-cyano-3,12-dioxooleana-1,9-dien-28-oate, that potently induces caspase-mediated apoptosis in human lung cancer cells
AUTHOR(S): Kim, Kevin B.; Lotan, Reuben; Yue, Ping; Sporn, Michael B.; Suh, Nanjoo; Gribble, Gordon W.; Honda, Tadashi; Wu, Gen Sheng; Hong, Waun Ki; Sun, Shi-Yong
CORPORATE SOURCE: Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Molecular Cancer Therapeutics (2002), 1(3), 177-184
CODEN: MCTOCF; ISSN: 1535-7163
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 05 Feb 2002
AB Lung cancer continues to be the leading cause of cancer-related death in the United States. Therefore, new agents targeting prevention and treatment of lung cancer are urgently needed. In the present study, we demonstrate that a novel synthetic triterpenoid methyl-2-cyano-3,12-dioxooleana-1,9-dien-28-oate (CDDO-Me) is a potent inducer of apoptosis in human non-small cell lung carcinoma (NSCLC) cells. The concns. required for a 50% decrease in cell survival (IC50) ranged from 0.1 to 0.3 .mu.M. CDDO-Me induced rapid apoptosis and triggered a series of effects assocd. with apoptosis including a rapid release of cytochrome c from mitochondria, activation of procaspase-9, -7, -6, and -3, and cleavage of poly(ADP-ribose) polymerase and lamin A/C. Moreover, the caspase-3 inhibitor Z-DEVD-FMK and the pan caspase inhibitor Z-VAD-FMK suppressed CDDO-Me-induced apoptosis. These results indicate that CDDO-Me induced apoptosis in human NSCLC cells via a cytochrome c-triggered caspase activation pathway. CDDO-Me did not alter the level of Bcl-2 and Bcl-xL proteins, and no correlation was found between cell sensitivity to CDDO-Me and basal Bcl-2 expression level. Furthermore, overexpression of Bcl-2 did not protect cells from CDDO-Me-induced apoptosis. These results suggest that CDDO-Me induces apoptosis in NSCLC cells irresp. of Bcl-2 expression level. In addn., no correlation was found between cell sensitivity to CDDO-Me and p53 status, suggesting that CDDO-Me induce a p53-independent apoptosis. Our results demonstrate that CDDO-Me may be a good candidate for addnl. evaluation as a potential therapeutic agent for human lung cancers and possibly other types of cancer.

IT **201556-11-8**, Procaspase-3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(identification of a novel synthetic triterpenoid, Me-2-cyano-3,12-dioxooleana-1,9-dien-28-oate, that potently induces caspase-mediated apoptosis in human lung cancer cells)

IT **218600-53-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(identification of a novel synthetic triterpenoid, Me-2-cyano-3,12-

dioxooleana-1,9-dien-28-oate, that potently induces caspase-mediated apoptosis in human lung cancer cells)
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L116 ANSWER 13 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 16
ACCESSION NUMBER: 2001:322933 CAPLUS
DOCUMENT NUMBER: 135:162202
TITLE: The novel triterpenoid CDDO induces apoptosis and differentiation of human osteosarcoma cells by a caspase-8 dependent mechanism
AUTHOR(S): Ito, Yasumasa; Pandey, Pramod; Sporn, Michael B.; Datta, Rakesh; Kharbanda, Surender; Kufe, Donald
CORPORATE SOURCE: Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA
SOURCE: Molecular Pharmacology (2001), 59(5), 1094-1099
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 07 May 2001
AB The oleanane triterpenoid 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO) is a multifunctional mol. that induces monocytic differentiation of human myeloid leukemia cells and inhibits proliferation of diverse human tumor cell lines. The present studies on human osteosarcoma cells demonstrate that CDDO induces mitochondrial cytochrome c release, caspase-3 activation, and internucleosomal DNA fragmentation. Overexpression of the caspase-8 inhibitor CrmA blocked CDDO-induced cytochrome c release and apoptosis. By contrast, overexpression of the antiapoptotic Bcl-xL protein blocked CDDO-induced cytochrome c release, but only partly inhibited caspase-3 activation and apoptosis. In concert with these findings, we demonstrate that CDDO: (1) activates caspase-8 and thereby caspase-3 by a cytochrome c-independent mechanism and (2) induces cytochrome c release by caspase-8-dependent cleavage of Bid. The results also demonstrate that treatment of osteosarcoma cells with CDDO induces differentiation, as assessed by alk. phosphatase activity and osteocalcin prodn., and that this response is abrogated in cells that overexpress CrmA. These findings demonstrate that CDDO induces both osteoblastic differentiation and apoptosis by caspase-8-dependent mechanisms.
IT **218600-44-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(triterpenoid CDDO induces apoptosis and differentiation of human osteosarcoma cells by a caspase-8 dependent mechanism)
IT **169592-56-7**, caspase-3 **179241-78-2**, caspase-8
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(triterpenoid CDDO induces apoptosis and differentiation of human osteosarcoma cells by a caspase-8 dependent mechanism)
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L116 ANSWER 14 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 18
ACCESSION NUMBER: 2000:392017 CAPLUS
DOCUMENT NUMBER: 133:114746
TITLE: The novel triterpenoid 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid induces apoptosis of human myeloid leukemia cells by a caspase-8-dependent mechanism
AUTHOR(S): Ito, Yasumasa; Pandey, Pramod; Place, Andrew; Sporn, Michael B.; Gribble, Gordon W.; Honda, Tadashi;

Kharbanda, Surender; Kufe, Donald
CORPORATE SOURCE: Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Cell Growth & Differentiation (2000), 11(5), 261-267
CODEN: CGDIE7; ISSN: 1044-9523
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 14 Jun 2000
AB The oleanane triterpenoid 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO) is a multifunctional mol. that induces growth inhibition and differentiation of human myeloid leukemia cells. The present studies demonstrate that CDDO treatment results in apoptosis of U-937 and HL-60 myeloid leukemia cells. Similar to 1-.beta.-D-arabinofuranosylcytosine (ara-C), another agent that inhibits growth and induces apoptosis of these cells, CDDO induced the release of mitochondrial cytochrome c and activation of caspase-3. Overexpression of Bcl-xL blocked cytochrome c release, caspase-3 activation, and apoptosis in ara-C-treated cells. By contrast, CDDO-induced release of cytochrome c, and activation of caspase-3 were diminished only in part by Bcl-xL. In concert with these findings, we demonstrate that CDDO, but not ara-C, activates caspase-8 and thereby caspase-3 by a cytochrome c-independent mechanism. The results also show that CDDO-induced cytochrome c release is mediated by caspase-8-dependent cleavage of Bid. These findings demonstrate that CDDO induces apoptosis of myeloid leukemia cells and that this novel agent activates an apoptotic signaling cascade distinct from that induced by the cytotoxic agent ara-C.
IT **169592-56-7**, Caspase-3
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(novel triterpenoid CDDO induces apoptosis of human myeloid leukemia cells)
IT **147-94-4**, Ara-C **179241-78-2**, Caspase-8
218600-44-3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(novel triterpenoid CDDO induces apoptosis of human myeloid leukemia cells)
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L116 ANSWER 15 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 19
ACCESSION NUMBER: 1999:811070 CAPLUS
DOCUMENT NUMBER: 132:44971
TITLE: Therapeutic triterpenoid compositions and methods of use for treatment of cancer, neurodegenerative, diseases, and inflammatory bowel diseases
INVENTOR(S): Gribble, Gordon W.; Honda, Tadashi; Sporn, Michael B.; Suh, Nanjoo
PATENT ASSIGNEE(S): Trustees of Dartmouth College, USA
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9965478	A1	19991223	WO 1999-US13635	19990618

W: CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

US 6326507	B1	20011204	US 1999-335003	19990617
CA 2335505	AA	19991223	CA 1999-2335505	19990618
EP 1089724	A1	20010411	EP 1999-928731	19990618
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002530272	T2	20020917	JP 2000-554358	19990618
US 2002042535	A1	20020411	US 2001-927081	20010809
US 6552075	B2	20030422		
US 2003236303	A1	20031225	US 2003-395372	20030324

PRIORITY APPLN. INFO.: US 1998-90053P P 19980619
US 1999-335003 A 19990617
WO 1999-US13635 W 19990618
US 2001-927081 A1 20010809

OTHER SOURCE(S): MARPAT 132:44971
ED Entered STN: 24 Dec 1999
AB Triterpenoid compds., e.g. 2-cyano-3,12-dioxoolean-1,9-dien--28-oic acid, and methods are disclosed which are useful for chemopreventative treatment of diseases such as cancer, Alzheimer's disease, Parkinson's disease, inflammatory bowel diseases, and multiple sclerosis.
IT **218600-53-4**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; triterpenoids for treatment of cancer, neurodegenerative, diseases, and inflammatory bowel diseases)
IT **218600-44-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(triterpenoids for treatment of cancer, neurodegenerative, diseases, and inflammatory bowel diseases)
IT **153559-76-3**, LG100268
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(triterpenoids for treatment of cancer, neurodegenerative, diseases, and inflammatory bowel diseases)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L116 ANSWER 16 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 20
ACCESSION NUMBER: 1999:71692 CAPLUS
DOCUMENT NUMBER: 130:261592
TITLE: A novel synthetic oleanane triterpenoid, 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid, with potent differentiating, antiproliferative, and anti-inflammatory activity
AUTHOR(S): Suh, Nanjoo; Wang, Yongping; Honda, Tadashi; Gribble, Gordon W.; Dmitrovsky, Ethan; Hickey, William F.; Maue, Robert A.; Place, Andrew E.; Porter, Donna M.; Spinella, Michael J.; Williams, Charlotte R.; Wu, Gengfei; Dannenberg, Andrew J.; Flanders, Kathleen C.; Letterio, John J.; Mangelsdorf, David J.; Nathan, Carl F.; Nguyen, Lananh; Porter, Weston W.; Ren, Renee F.; Roberts, Anita B.; Roche, Nanette S.; Subbaramaiah, Kotha; Sporn, Michael B.
CORPORATE SOURCE: Norris Cotton Cancer Center, Department of Pharmacology, Dartmouth Medical School, Hanover, NH, 03755, USA
SOURCE: Cancer Research (1999), 59(2), 336-341
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: Journal
LANGUAGE: English

ED Entered STN: 03 Feb 1999
AB The new synthetic oleanane triterpenoid 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO) is a potent, multifunctional mol. It induces monocytic differentiation of human myeloid leukemia cells and adipogenic differentiation of mouse 3T3-L1 fibroblasts and enhances the neuronal differentiation of rat PC12 pheochromocytoma cells caused by nerve growth factor. CDDO inhibits proliferation of many human tumor cell lines, including those derived from estrogen receptor-pos. and -neg. breast carcinomas, myeloid leukemias, and several carcinomas bearing a Smad4 mutation. Furthermore, it suppresses the abilities of various inflammatory cytokines, such as IFN-.gamma., interleukin-1, and tumor necrosis factor-.alpha., to induce de novo formation of the enzymes inducible nitric oxide synthase (iNos) and inducible cyclooxygenase (COX-2) in mouse peritoneal macrophages, rat brain microglia, and human colon fibroblasts. CDDO will also protect rat brain hippocampal neurons from cell death induced by .beta.-amyloid. The above activities have been found at concns. ranging from 10-6 to 10-9 M in cell culture, and these results suggest that CDDO needs further study in vivo, for either chemoprevention or chemotherapy of malignancy as well as for neuroprotection.
IT **218600-44-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthetic oleanane triterpenoid cyano-dioxoolean-dien-oic acid: differentiating, antiproliferative, and anti-inflammatory activity)
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L116 ANSWER 17 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:212705 CAPLUS
DOCUMENT NUMBER: 140:332100
TITLE: Peroxisome proliferator-activated receptor-.gamma.-independent repression of collagenase gene expression by 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid and prostaglandin 15-deoxy-.DELTA.(12,14) J2: a role for Smad signaling
AUTHOR(S): Mix, Kimberlee S.; Coon, Charles I.; Rosen, Evan D.; Suh, Nanjoo; Sporn, Michael B.; Brinckerhoff, Constance E.
CORPORATE SOURCE: Department of Biochemistry, Dartmouth Medical School, Hanover, NH, USA
SOURCE: Molecular Pharmacology (2004), 65(2), 309-318
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 17 Mar 2004
AB Matrix metalloproteinases (MMPs) degrade extracellular matrix components, and overexpression of these enzymes contributes to tissue destruction in arthritis. Of particular importance are the collagenases, MMP-1 and MMP-13, which have high activity against the interstitial collagens in cartilage. In this study, we address the mechanisms of two inhibitors of collagenase gene expression, the synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) and 15-deoxy-.DELTA.(12,14)-prostaglandin J2 (15-dPGJ2). Although both inhibitors are ligands for the nuclear hormone receptor peroxisome proliferator-activated receptor-.gamma. (PPAR-.gamma.), a connection between PPAR-.gamma. and collagenase gene expression has yet to be established. Here, we test the hypothesis that CDDO and 15-dPGJ2 use PPAR-.gamma. to repress MMP gene expression. Our findings with the

PPAR-.gamma. antagonist 2-[4-[2-[3-(2,4-difluorophenyl)-1-heptylureido]ethyl]-phenylsulfanyl]-2-methylpropionic acid (GW9662) and mouse embryonic fibroblasts lacking PPAR-.gamma. demonstrate that CDDO and 15-dPGJ2 use PPAR-.gamma.-independent mechanisms to inhibit collagenase gene expression. To address a potential PPAR-.gamma.-independent mechanism leading to the repression of MMPs by CDDO, we tested the effect of CDDO on the transforming growth factor-.beta. (TGF-.beta.) signaling pathway. We found that CDDO requires Smads (transcription factors activated by TGF-.beta.) for the repression of MMP-1. Specifically, MMP-1 is inhibited neither by CDDO in the absence of TGF-.beta. receptor-activated Smad3 nor when a neg. regulator, Smad7, attenuates TGF-.beta. signaling. We conclude that CDDO represses MMP gene expression through a novel PPAR-.gamma.-independent mechanism that requires Smad signaling.

IT **218600-44-3**, CDDO
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); BIOL (Biological study)
(role of Smad signalling in PPAR-.gamma.-independent repression of collagenase gene expression by collagenase inhibitors)

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L116 ANSWER 18 OF 49 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:298975 CAPLUS
DOCUMENT NUMBER: 137:241873
TITLE: Differentiating and anti-inflammatory activities of the triterpenoid, CDDO: interactions with transcription factors PPAR-.gamma. and NF-.kappa.B
AUTHOR(S): Wang, Yongping
CORPORATE SOURCE: Dartmouth College, Hanover, NH, USA
SOURCE: (2001) 152 pp. Avail.: UMI, Order No. DA3015490 From: Diss. Abstr. Int., B 2001, 62(5), 2276
DOCUMENT TYPE: Dissertation
LANGUAGE: English
ED Entered STN: 22 Apr 2002
AB Unavailable
IT **218600-44-3**, CDDO
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(differentiating and anti-inflammatory activities of the triterpenoid, CDDO: interactions with transcription factors PPAR-.gamma. and NF-.kappa.B)

L116 ANSWER 19 OF 49 USPATFULL on STN DUPLICATE 1
ACCESSION NUMBER: 2004:2440 USPATFULL
TITLE: Inhibitors and methods of use thereof
INVENTOR(S): Honda, Tadashi, Hanover, NH, UNITED STATES
Honda, Yukiko, Hanover, NH, UNITED STATES
Gribble, Gordon W., Lebanon, NH, UNITED STATES
Sporn, Michael B., Tunbridge, VT, UNITED STATES
Suh, Nanjoo, White River Junction, VT, UNITED STATES
PATENT ASSIGNEE(S): The Trustees of Dartmouth College (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004002463	A1	20040101	
APPLICATION INFO.:	US 2003-435925	A1	20030512	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-378009P	20020513 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FULBRIGHT & JAWORSKI L.L.P., 600 CONGRESS AVE., SUITE 2400, AUSTIN, TX, 78701
NUMBER OF CLAIMS: 65
EXEMPLARY CLAIM: 1
LINE COUNT: 1106
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB New triterpenoid derivatives with various substituents at the C-17 position of 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) were synthesized. Among them, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile (CNDDO), 1-(2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl) imidazole, 1-(2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl)-2-methylimidazole, 1-(2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl)-4-methylimidazole show extremely high inhibitory activity (IC.sub.50=0.01-1 pM level) against production of nitric oxide induced by interferon-.gamma. in mouse macrophages. These compounds can be used in the prevention or treatment of diseases such as cancer, Alzheimer's disease, Parkinson's disease, multiple sclerosis, rheumatoid arthritis, and other inflammatory diseases. All the new triterpenoid derivatives are more potent than previously known CDDO.
IT **218600-44-3**
(prepn. of triterpenoid derivs. as inhibitors of nitric oxide prodn.)

L116 ANSWER 20 OF 49 USPATFULL on STN
ACCESSION NUMBER: 2003:335425 USPATFULL
TITLE: Therapeutic compositions and methods of use
INVENTOR(S): Gribble, Gordon W., Norwich, VT, UNITED STATES
Honda, Tadashi, Hanover, NH, UNITED STATES
Sporn, Michael B., Tunbridge, VT, UNITED STATES
Suh, Nanjoo, Hanover, NH, UNITED STATES
PATENT ASSIGNEE(S): Trustees of Darmouth College (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003236303	A1	20031225
APPLICATION INFO.:	US 2003-395372	A1	20030324 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-927081, filed on 9 Aug 2001, GRANTED, Pat. No. US 6552075 Division of Ser. No. US 1999-335003, filed on 17 Jun 1999, GRANTED, Pat. No. US 6326507

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-90053P	19980619 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Steven L. Highlander, Esq., FULBRIGHT & JAWORSKI L.L.P., Suite 2400, 600 Congress Avenue, Austin, TX, 78701
NUMBER OF CLAIMS: 73
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 1146
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds and methods useful for chemopreventative treatment of diseases such as cancer, Alzheimer's disease, Parkinson's disease, inflammatory bowel diseases, and multiple sclerosis.
IT **218600-53-4**
(reaction; triterpenoids for treatment of cancer, neurodegenerative, diseases, and inflammatory bowel diseases)
IT **218600-44-3P**
(triterpenoids for treatment of cancer, neurodegenerative, diseases,

and inflammatory bowel diseases)

L116 ANSWER 21 OF 49 USPATFULL on STN
ACCESSION NUMBER: 2003:173884 USPATFULL
TITLE: CDDO-compounds and combination therapies thereof
INVENTOR(S): Konopleva, Marina, Houston, TX, UNITED STATES
Andreeff, Michael, Houston, TX, UNITED STATES
Sporn, Michael B., Tunbridge, VT, UNITED STATES
PATENT ASSIGNEE(S): Board of (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003119732	A1	20030626
APPLICATION INFO.:	US 2001-998009	A1	20011128 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-253673P	20001128 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Priya D. Subramony, Fulbright & Jaworski L.L.P., 600 Congress Avenue, Suite 2400, Austin, TX, 78701
NUMBER OF CLAIMS: 79
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 35 Drawing Page(s)
LINE COUNT: 5276
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB CDDO-compounds in combination with other chemotherapeutic agents induce and potentiate cytotoxicity and apoptosis in cancer cell. One class of chemotherapeutic agents include retinoids. Cancer therapies based on these combination therapies are provided. Also provided are methods to treat graft versus host diseases using the CDDO compounds.
IT **218600-44-3 218600-53-4**
(CDDO compds. and combinations with other chemotherapeutics for treatment of cancer and graft vs. host disease)
IT **218600-44-3D**, derivs.
(CDDO compds. and combinations with other chemotherapeutics for treatment of cancer and graft vs. host disease)

L116 ANSWER 22 OF 49 USPATFULL on STN
ACCESSION NUMBER: 2002:78876 USPATFULL
TITLE: Therapeutic compounds and methods of use
INVENTOR(S): Gribble, Gordon W., Norwich, VT, UNITED STATES
Honda, Tadashi, Hanover, NH, UNITED STATES
Sporn, Michael B., Tunbridge, VT, UNITED STATES
Suh, Nanjoo, Hanover, NH, UNITED STATES
PATENT ASSIGNEE(S): Trustees of Dartmouth College (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002042535	A1	20020411
	US 6552075	B2	20030422
APPLICATION INFO.:	US 2001-927081	A1	20010809 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1999-335003, filed on 17 Jun 1999, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-90053P	19980619 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Steven L. Highlander, FULBRIGHT & JAWORSKI L.L.P.,

Suite 2400, 600 Congress Avenue, Austin, TX, 78701
NUMBER OF CLAIMS: 73
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Page(s)
LINE COUNT: 1150
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds and methods useful for chemopreventative treatment of diseases such as cancer, Alzheimer's disease, Parkinson's disease, inflammatory bowel diseases, and multiple sclerosis.
IT **218600-53-4**
(reaction; triterpenoids for treatment of cancer, neurodegenerative, diseases, and inflammatory bowel diseases)
IT **218600-44-3P**
(triterpenoids for treatment of cancer, neurodegenerative, diseases, and inflammatory bowel diseases)

L116 ANSWER 23 OF 49 USPATFULL on STN
ACCESSION NUMBER: 2001:221178 USPATFULL
TITLE: Therapeutic compounds and methods of use
INVENTOR(S): Gribble, Gordon W., Norwich, VT, United States
Honda, Tadashi, Hanover, NH, United States
Sporn, Michael B., Tunbridge, VT, United States
Suh, Nanjoo, Hanover, NH, United States
PATENT ASSIGNEE(S): Trustees of Dartmouth College, Hanover, NH, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6326507	B1	20011204
APPLICATION INFO.:	US 1999-335003		19990617 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-90053P	19980619 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Higel, Floyd D.
ASSISTANT EXAMINER: Sackey, Ebenezer
LEGAL REPRESENTATIVE: Fulbright & Jaworski, LLP
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Figure(s); 11 Drawing Page(s)
LINE COUNT: 964
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds and methods useful for chemopreventative treatment of diseases such as cancer, Alzheimer's disease, Parkinson's disease, inflammatory bowel diseases, and multiple sclerosis.
IT **218600-53-4**
(reaction; triterpenoids for treatment of cancer, neurodegenerative, diseases, and inflammatory bowel diseases)
IT **218600-44-3P**
(triterpenoids for treatment of cancer, neurodegenerative, diseases, and inflammatory bowel diseases)

L116 ANSWER 24 OF 49 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2004176476 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15070698
TITLE: The bortezomib/proteasome inhibitor PS-341 and triterpenoid **CDDO**-Im induce synergistic anti-multiple myeloma

(MM) activity and overcome bortezomib resistance.

AUTHOR: Chauhan Dharminder; Li Guilan; Podar Klaus; Hideshima Teru; Shringarpure Reshma; Catley Laurence; Mitsiades Constantine; Munshi Nikhil; Tai Yu Tzu; Suh Nanjoo; Gribble Gordon W; Honda Tadashi; Schlossman Robert; Richardson Paul; Sporn Michael B; Anderson Kenneth C

CORPORATE SOURCE: Jerome Lipper Multiple Myeloma Center, Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02215, USA.

CONTRACT NUMBER: 50947 (NCI)
CA 78373 (NCI)
CA 78814 (NCI)
P01 CA078378-06 (NCI)
P50 CA100707-01

SOURCE: Blood, (2004 Apr 15) 103 (8) 3158-66.
Journal code: 7603509. ISSN: 0006-4971.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 20040409
Last Updated on STN: 20040528
Entered Medline: 20040527

ABSTRACT:
The synthetic triterpenoid 2-cyano-3, 12-dioxooleana-1, 9-dien-28-oic acid (***CDDO***) induces apoptosis in leukemic cells. Here we show that ***CDDO*** and its new derivative **CDDO**-imidazolide (**CDDO**-Im) trigger apoptosis in multiple myeloma (MM) cells resistant to conventional therapies including melphalan (LR-5), doxorubicin (Dox-40), and dexamethasone (MM.1R, U266, RPMI 8226) without affecting the viability of normal cells. ***CDDO*** -IM also triggers apoptosis in bone marrow stromal cells (BMSCs) and decreases interleukin-6 (IL-6) secretion induced by MM cell adhesion to BMSCs. Moreover, **CDDO**-Im-induced apoptosis in MM cells is not blocked by IL-6 or insulin growth factor-1 (IGF-1). Importantly, **CDDO**-Im and bortezomib/proteasome inhibitor PS-341 trigger synergistic apoptosis in MM cells associated with loss of mitochondrial membrane potential, superoxide generation, release of mitochondrial proteins cytochrome c/second mitochondria-derived activator of caspases (cytochrome c/Smac), and activation of caspase-8, -9, and -3. Conversely, the pancaspase inhibitor Z-VAD-fmk abrogates the **CDDO**-Im + bortezomib-induced apoptosis. Low doses of ***CDDO*** -Im and bortezomib overcome the cytoprotective effects of antiapoptotic proteins Bcl2 and heat shock protein-27 (Hsp27) as well as nuclear factor-kappa B (NF-kappaB)-mediated growth/survival and drug resistance. Finally, combining **CDDO**-Im and bortezomib induces apoptosis even in bortezomib-resistant MM patient cells. Together, these findings provide the framework for clinical evaluation of **CDDO**-Im, either alone or in combination with bortezomib, to overcome drug resistance and improve patient outcome in MM.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Antineoplastic Combined Chemotherapy Protocols: AD, administration & dosage
Apoptosis: DE, drug effects
Bone Marrow Cells: DE, drug effects
Bone Marrow Cells: PA, pathology
Bone Marrow Cells: PH, physiology
*Boronic Acids: AD, administration & dosage
Cell Division: DE, drug effects
Cell Line, Tumor
Drug Resistance, Neoplasm
Drug Synergism

Genes, bcl-2
*Imidazoles: AD, administration & dosage
Insulin-Like Growth Factor I: PD, pharmacology
Interleukin-6: BI, biosynthesis
Lymphocytes: DE, drug effects
Membrane Potentials: DE, drug effects
Mitochondria: DE, drug effects
Mitochondria: ME, metabolism
*Multiple Myeloma: DT, drug therapy
Multiple Myeloma: GE, genetics
Multiple Myeloma: PA, pathology
Multiple Myeloma: PP, physiopathology
Mutation
NF-kappa B: GE, genetics
*Oleanolic Acid: AD, administration & dosage
*Oleanolic Acid: AA, analogs & derivatives
Protease Inhibitors: AD, administration & dosage
*Pyrazines: AD, administration & dosage
Recombinant Proteins: PD, pharmacology
Transfection

CAS REGISTRY NO.: 508-02-1 (Oleanolic Acid); 67763-96-6 (Insulin-Like Growth Factor I)

CHEMICAL NAME: 0 (1-(2-cyano-3,12-dioxooleana-1,9-dien-28-oyl) imidazole); 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (Boronic Acids); 0 (Imidazoles); 0 (Interleukin-6); 0 (NF-kappa B); 0 (Protease Inhibitors); 0 (Pyrazines); 0 (Recombinant Proteins); 0 (bortezomib)

L116 ANSWER 25 OF 49 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 2000491121 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11043571
TITLE: A synthetic triterpenoid, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (**CDDO**), is a ligand for the peroxisome proliferator-activated receptor gamma.
AUTHOR: Wang Y; Porter W W; Suh N; Honda T; Gribble G W; Leesnitzer L M; Plunket K D; Mangelsdorf D J; Blanchard S G; Willson T M; Sporn M B
CORPORATE SOURCE: Department of Pharmacology, Dartmouth Medical School and Dartmouth College, Hanover, New Hampshire 03755, USA.
CONTRACT NUMBER: R01 CA-78814 (NCI)
SOURCE: Molecular endocrinology (Baltimore, Md.), (2000 Oct) 14 (10) 1550-6.
Journal code: 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20030318
Entered Medline: 20010208

ABSTRACT:
A novel synthetic triterpenoid, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (***CDDO***), previously reported to have potent differentiating, antiproliferative, and antiinflammatory activities, has been identified as a ligand for the peroxisome proliferator-activated receptor gamma (PPARgamma). ***CDDO*** induces adipocytic differentiation in 3T3-L1 cells, although it is not as potent as the full agonist of PPARgamma, rosiglitazone. Binding studies of **CDDO** to PPARgamma using a scintillation proximity assay give a Ki between 10(-8) to 10(-7) M. In transactivation assays, **CDDO** is a partial agonist for PPARgamma. The methyl ester of **CDDO**, ***CDDO*** -Me, binds to PPARgamma with similar affinity, but is an

antagonist. Like other PPARgamma ligands, **CDDO** synergizes with a retinoid X receptor (RXR)-specific ligand to induce 3T3-L1 differentiation, while **CDDO**-Me is an antagonist in this assay. The partial agonism of ***CDDO*** and the antagonism of **CDDO**-Me reflect the differences in their capacity to recruit or displace cofactors of transcriptional regulation; ***CDDO*** and rosiglitazone both release the nuclear receptor corepressor, NCoR, from PPARgamma, while **CDDO**-Me does not. The differences between **CDDO** and rosiglitazone as either partial or full agonists, respectively, are seen in the weaker ability of **CDDO** to recruit the coactivator CREB-binding protein, CBP, to PPARgamma. Our results establish the triterpenoid **CDDO** as a member of a new class of PPARgamma ligands.

CONTROLLED TERM: Check Tags: Comparative Study; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
3T3 Cells
Adipocytes: CY, cytology
Animals
Cell Differentiation: DE, drug effects
Drug Synergism
Ligands
Methylation
Mice
Nicotinic Acids: PD, pharmacology
Nuclear Proteins: ME, metabolism
*Oleanolic Acid: AA, analogs & derivatives
*Oleanolic Acid: ME, metabolism
Oleanolic Acid: PD, pharmacology
Receptors, Cytoplasmic and Nuclear: AG, agonists
Receptors, Cytoplasmic and Nuclear: AI, antagonists & inhibitors
*Receptors, Cytoplasmic and Nuclear: ME, metabolism
Receptors, Retinoic Acid: ME, metabolism
Repressor Proteins: ME, metabolism
Tetrahydronaphthalenes: PD, pharmacology
Thiazoles: PD, pharmacology
*Thiazolidinediones
Trans-Activation (Genetics)
Trans-Activators: ME, metabolism
Transcription Factors: AG, agonists
Transcription Factors: AI, antagonists & inhibitors
*Transcription Factors: ME, metabolism

CAS REGISTRY NO.: 122320-73-4 (rosiglitazone); 508-02-1 (Oleanolic Acid)

CHEMICAL NAME: 0 (2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid); 0 (CREB-binding protein); 0 (LG 100268); 0 (Ligands); 0 (Nicotinic Acids); 0 (Nuclear Proteins); 0 (Receptors, Cytoplasmic and Nuclear); 0 (Receptors, Retinoic Acid); 0 (Repressor Proteins); 0 (Tetrahydronaphthalenes); 0 (Thiazoles); 0 (Thiazolidinediones); 0 (Trans-Activators); 0 (Transcription Factors); 0 (nuclear receptor co-repressor); 0 (peroxisome proliferator-activated receptor); 0 (retinoid X receptor)

L116 ANSWER 26 OF 49 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 2003-08746 DRUGU P V

TITLE: Chromatin-mediated transcriptional activation with novel peroxisome proliferator-activated receptor gamma (PPARgamma) ligand 2-cyano-3,12-dioxooleana- 1,9-dien-28-oic acid (**CDDO**) in acute promyelocytic leukemia cells.

AUTHOR: Tabe Y; Konopleva M; Tsao T; Lapillonne H; Jackson C E E; Andreeff M

CORPORATE SOURCE: Univ.Texas-Syst.M.D.Anderson-Cancer-Cent.

LOCATION: Houston, Tex., USA

SOURCE: Blood (100, No. 11, Pt. 1, 557a-558a, 2002)

CODEN: BLOOAW ISSN: 0006-4971
AVAIL. OF DOC.: Blood and Marrow, Transplantation, The University of Texas M.D. Anderson Cancer Center, Houston, TX, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

The PPARgamma ligand 2-cyano-3,12-dioxooleana- 1,9-dien-28-oic acid (***CDDO*** ; TP-151) induced histone modifications in the RARbeta P2 and p21WAF1 promoter regions in acute promyelocytic leukemia (APL) cells. In combination with tretinoin (ATRA), **CDDO** induced maximal transcriptional activation by stimulating histone acetylation/methylation with recruitment of p300/CBP that overcame the chromatin-mediated transcriptional repression in APL cells. This resulted in enhanced expression of RARbeta and p21WAF1 mRNA, in induction of differentiation and apoptosis in ATRA-resistant APL cells. The data establish, for the first time, the paradigm of combined activation of RARalpha and PPARgamma as basis for 'targeted transcription therapy' in APL. (conference abstract: 44th Annual Meeting of the American Society of Hematology, Philadelphia, Pennsylvania, USA, 2002).

SECTION HEADING: P Pharmacology
V Vitamins

CLASSIF. CODE: 42 Vitamins
52 Chemotherapy - non-clinical
66 Drug Interactions
73 Trial Preparations

CONTROLLED TERM:
IN-VITRO *FT; ACUTE *FT; PROMYELOCYTIC *FT; LEUKEMIA *FT; TUMOR-CELL *FT; NB4-CELL *FT; U937-CELL *FT; ALONE *FT; **COMB.** *FT; DRUG-COMPARISON *FT; APOPTOSIS *FT; DIFFERENTIATION *FT; RETINOID-RECEPTOR *FT; ONCOGENE *FT; TRANSCRIPTION *FT; MESSENGER *FT; RNA *FT; CYTOSTATIC *FT; APOPTOSIS-INDUCER *FT; TISSUE-CULTURE *FT; RECEPTOR *FT; GENE *FT; GENETICS *FT
[01] TP-151 *TR; TP-151 *DI; DR9807631 *RN; TRETINOIN *DI; ANTIINFLAMMATORIES *FT; APOPTOSIS-INDUCERS *FT; CYCLOOXYGENASE-2-INHIBITORS *FT; CYTOSTATICS *FT; HEMOSTATICS *FT; MATRIX-METALLOPROTEINASE-INHIBITORS *FT; NITRIC-OXIDE-ANTAGONISTS *FT; SYNERGISTS *FT; TRIAL-PREP. *FT; PROSTAGLANDIN-ANTAGONISTS *FT; CYCLOOXYGENASE-INHIBITORS *FT; TR *FT; DI *FT
[02] TRETINOIN *PH; TRETINOIN *DI; TP-151 *DI; TRETINOIN *RN; ANGIOGENESIS-INHIBITORS *FT; KERATOLYTICS *FT; VITAMINS-A *FT; ORNITHINE-DECARBOXYLASE-INHIBITORS *FT; ALKALINE-PHOSPHATASE-INHIBITORS *FT; PH *FT; DI *FT
CAS REGISTRY NO.: 302-79-4
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L116 ANSWER 27 OF 49 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-45753 DRUGU B P E
TITLE: Selected PPARg ligands sensitize tumor cells to death receptor-mediated apoptosis.
AUTHOR: Kim Y; Sporn M; Reed J C
CORPORATE SOURCE: Dartmouth-Med.Sch.; Burnham-Inst.
LOCATION: Hanover, N.H.; La Jolla, Cal., USA
SOURCE: Proc.Am.Assoc.Cancer Res. (42, 92 Meet., 129, 2001) ISSN: 0197-016X
AVAIL. OF DOC.: Dartmouth Medical School, Hanover, NH, U.S.A.

LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

The effects of a synthetic triterpenoid, **CDDO** and 15-delta-PGJ2 were studied in tumor cells. In combination with TRAIL, **CDDO** or 15-delta-PGJ2 induced a robust apoptosis in TRAIL-resistant epithelial cancer cell lines. Experiments with a PPAR-gamma-negative cell line suggested that 15-delta-PGJ2 and **CDDO** down-regulated the anti-apoptotic protein c-FLIP and sensitized cells to TRAIL-induced apoptosis independent of PPAR-gamma. Taken together, these results suggest that compounds that inhibit c-FLIP expression should be considered for use in clinical trials in combination with TRAIL for sensitizing refractory cancers to TRAIL-induced apoptosis. (conference abstract: 92nd Annual Meeting of the American Association for Cancer Research, New Orleans, Louisiana, USA, 2001).

SECTION HEADING: B Biochemistry
P Pharmacology
E Endocrinology

CLASSIF. CODE: 27 Molecular Biology
48 Prostaglandins
50 Biological Response Modifiers
52 Chemotherapy - non-clinical
66 Drug Interactions
73 Trial Preparations

CONTROLLED TERM:
CYTOSTATIC *FT; APOPTOSIS-INDUCER *FT; **COMB.** *FT; SYNERGIST *FT; IN-VITRO *FT; TUMOR-CELL *FT; RESISTANT *FT; APOPTOSIS *FT; NUCLEAR-FACTOR-KAPPA-B *FT; NF-KAPPA-B *FT; MODE-OF-ACT. *FT; DOWN-REGULATION *FT; TISSUE-CULTURE *FT
[01] PGJ2-DEOXY-15-DELTA-12,14 *PH; PGJ2-DEOXY-15-DELTA-12,14 *DI; DR9710353 *RN; TNF-RELATED-APOPTOSIS-INDUCING-LIGAND *DI; TUMOR-NECROSIS-FACTOR-ALPHA *DI; APOPTOSIS-INDUCERS *FT; CYTOSTATICS *FT; PPAR-AGONISTS *FT; PROSTAGLANDINS *FT; PH *FT; DI *FT
[02] TNF-RELATED-APOPTOSIS-INDUCING-LIGAND *PH; TNF-RELATED-APOPTOSIS-INDUCING-LIGAND *DI; DR9701079 *RN; PGJ2-DEOXY-15-DELTA-12,14 *DI; TP-151 *DI; APOPTOSIS-INDUCERS *FT; CYTOSTATICS *FT; PH *FT; DI *FT
[03] TP-151 *PH; TP-151 *DI; DR9807631 *RN; TNF-RELATED-APOPTOSIS-INDUCING-LIGAND *DI; TUMOR-NECROSIS-FACTOR-ALPHA *DI; ANTIINFLAMMATORIES *FT; APOPTOSIS-INDUCERS *FT; CYCLOOXYGENASE-2-INHIBITORS *FT; CYTOSTATICS *FT; HEMOSTATICS *FT; MATRIX-METALLOPROTEINASE-INHIBITORS *FT; NITRIC-OXIDE-ANTAGONISTS *FT; SYNERGISTS *FT; TRIAL-PREP. *FT; PROSTAGLANDIN-ANTAGONISTS *FT; CYCLOOXYGENASE-INHIBITORS *FT; PH *FT; DI *FT
[04] TUMOR-NECROSIS-FACTOR-ALPHA *PH; TUMOR-NECROSIS-FACTOR-ALPHA *DI; TP-151 *DI; PGJ2-DEOXY-15-DELTA-12,14 *DI; TUMORNEFA *RN; CYTOSTATICS *FT; PH *FT; DI *FT

FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L116 ANSWER 28 OF 49 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-14068 DRUGU P
TITLE: Triterpenoids **CDDO** and **CDDO**-Me down-regulate FLIP expression and sensitize AML cells to TRAIL-induced apoptosis.
AUTHOR: Suh W S; Shinichi K; Kim Y; Andreeff M; Sporn M; Suh N; Reed

J C
CORPORATE SOURCE: Inst.Burnham; Anderson-Cancer-Cent.; Dartmouth-Med.Sch.
LOCATION: La Jolla, Cal., Houston, Tex.; Hanover, N.H., USA
SOURCE: Blood (98, No. 11, Pt. 1, 118a-119a, 2001)
CODEN: BLOOAW ISSN: 0006-4971
AVAIL. OF DOC.: The Burnham Institute, La Jolla, CA, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

CDDO (TP-151) and its methyl ester (**CDDO**-Me) reduced the viability of HL-60, U-937 and AML-2 cells in a dose-dependent manner. This loss of cell viability was attributed to apoptosis. **CDDO** and ***CDDO*** -Me induced rapid reductions in the levels of FLIP protein. ***CDDO*** and **CDDO**-Me down-regulated FLIP and rendered cell lines sensitive to TRAIL. Apoptosis of peripheral blood lymphocytes and normal bone marrow cells was not triggered by **CDDO**, **CDDO**-Me, TRAIL or combinations of these agents. Triterpenoids warrant investigation in the treatment of AML, alone or in combination with TRAIL or other immune-based therapies. (conference abstract: 43rd Annual Meeting of the American Society of Hematology, Orlando, Florida, USA, 2001).

SECTION HEADING: P Pharmacology

CLASSIF. CODE: 50 Biological Response Modifiers
52 Chemotherapy - non-clinical
73 Trial Preparations

CONTROLLED TERM:
IN-VITRO *FT; EXPRESSION *FT; APOPTOSIS *FT; APOPTOSIS-INDUCER *FT; CYTOSTATIC *FT; HL60-CELL *FT; U937-CELL *FT; TUMOR-CELL *FT; AML2-CELL *FT; **COMB.** *FT; TISSUE-CULTURE *FT; LEUKEMIA *FT; TUMOR-CELL *FT; TISSUE-CULTURE *FT
[01] TPI-151 *PH; DR9807631 *RN; ANTIINFLAMMATORIES *FT; APOPTOSIS-INDUCERS *FT; CYCLOOXYGENASE-2-INHIBITORS *FT; CYTOSTATICS *FT; HEMOSTATICS *FT; MATRIX-METALLOPROTEINASE-INHIBITORS *FT; SYNERGISTS *FT; TRIAL-PREP. *FT; NITRIC-OXIDE-ANTAGONISTS *FT; PROSTAGLANDIN-ANTAGONISTS *FT; CYCLOOXYGENASE-INHIBITORS *FT; PH *FT
[02] DR0013131 *RN; PH *FT
[03] TNF-RELATED-APOPTOSIS-INDUCING-LIGAND *PH; DR9701079 *RN; APOPTOSIS-INDUCERS *FT; CYTOSTATICS *FT; PH *FT
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L116 ANSWER 29 OF 49 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2000-15626 DRUGU P
TITLE: Novel synthetic triterpenoid, **CDDO**, and its methyl ester: potent antiproliferative, proapoptotic and differentiating agents in AML.
AUTHOR: Konopleva M; Estrov Z; Stiouf I; Chang S; Zhao S; Harris D; Leysath C; Xie Z; Jackson E; Hong W K
CORPORATE SOURCE: Univ.Texas-Syst.; Dartmouth-Coll.
LOCATION: Houston, Tex.; Hanover, N.H., USA
SOURCE: Blood (94, No. 10, Pt. 1 Suppl. 1, 479a, 1999)
CODEN: BLOOAW ISSN: 0006-4971
AVAIL. OF DOC.: Molecular Hematology and Therapy, The University of Texas M. D. Anderson Cancer Center, Houston, TX, U.S.A. (16 authors).
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

CDDO (TP-151) and its methyl ester (**CDDO**-m) were confirmed to be Mdr-1-independent compounds that exerted strong antiproliferative, apoptotic and differentiating effects on leukemic cell lines, primary AML and blast crisis of CML in-vitro. The apoptotic effect was mediated by the induction of Bax expression, decrease in the mitochondrial membrane potential, expression of phosphatidyl serine on the cell surface followed by activation of caspase-3 and cleavage of downstream substrates. **CDDO** synergistically induced differentiation in combination with tretinoin (ATRA). ***CDDO*** enhanced cytarabine (Ara-C)-induced apoptosis. Differential effects on leukemic and normal progenitor cells suggest potential efficacy of ***CDDO*** in the treatment of hematologic malignancies. (conference abstract: 41st Annual Meeting of the American Society of Hematology, New Orleans, Louisiana, USA, 1999).

SECTION HEADING: P Pharmacology

CLASSIF. CODE: 52 Chemotherapy - non-clinical
66 Drug Interactions
73 Trial Preparations

CONTROLLED TERM:
IN-VITRO *FT; HL60-CELL *FT; U937-CELL *FT; THP1-CELL *FT; MOE7-CELL *FT; K562-CELL *FT; ERYTHROLEUKEMIA *FT; APOPTOSIS *FT; PROLIFERATION *FT; DIFFERENTIATION *FT; CYTOSTATIC *FT; ALONE *FT; **COMB.** *FT; DRUG-COMPARISON *FT; SYNERGIST *FT; PROGENITOR *FT; MYELOID *FT; MITOCHONDRIA *FT; MEMBRANE-POTENTIAL *FT; BAX *FT; GENE *FT; EXPRESSION *FT; APOPTOSIS-INDUCER *FT; TISSUE-CULTURE *FT; LEUKEMIA *FT; TUMOR-CELL *FT; SUBCELL.STRUCT. *FT; ELECTROPHYSIOL. *FT; GENETICS *FT

[01] TP-151 *PH; TP-151 *DI; DR9807631 *RN; CYTARABINE *DI; TRETINOIN *DI; MODE-OF-ACT. *FT; TRIAL-PREP. *FT; SYNERGISTS *FT; NITRIC-OXIDE-ANTAGONISTS *FT; HEMOSTATICS *FT; CYTOSTATICS *FT; PH *FT; DI *FT

[02] DR0013131 *RN; CYTARABINE *DI; TRETINOIN *DI; MODE-OF-ACT. *FT; PH *FT; DI *FT

[03] CYTARABINE *PH; CYTARABINE *DI; CYTARABIN *RN; CYTOSTATICS *FT; VIRUCIDES *FT; PH *FT; DI *FT

CAS REGISTRY NO.: 147-94-4

[04] TRETINOIN *PH; TRETINOIN *DI; TRETINOIN *RN; ANGIOGENESIS-INHIBITORS *FT; KERATOLYTICS *FT; VITAMINS-A *FT; ORNITHINE-DECARBOXYLASE-INHIBITORS *FT; ALKALINE-PHOSPHATASE-INHIBITORS *FT; PH *FT; DI *FT

CAS REGISTRY NO.: 302-79-4
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L116 ANSWER 30 OF 49 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1990-38297 DRUGU P
TITLE: Synergistic Cytotoxicity Using 2+-Deoxy-5-Azacytidine and Cisplatin or 4-Hydroperoxycyclo- phosphamide with Human Tumor Cells.
AUTHOR: Frost P; Abbruzzese J L; Hunt B; Lee D; Ellis M
LOCATION: Houston, Texas, United States
SOURCE: Cancer Res. (50, No. 15, 4572-77, 1990) 3 Fig. 4 Tab. 36 Ref.
CODEN: CNREA8 ISSN: 0008-5472
AVAIL. OF DOC.: Department of Cell Biology, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Box 173, Houston, TX 77030, U.S.A.

LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

The combined use of 2+-deoxy-5-azacytidine (DAC, Pharmachemie) with cisplatin (cDDP) or 4-hydroperoxycyclo- phosphamide (4-HC) in vitro frequently resulted in synergistic cytotoxicity against a panel of 6 human tumor cell lines. This enhanced killing was seen at concentrations that are clinically achievable. There was no clear correlation between the degree of DNA hypomethylation observed and the induction of synergy. By contrast, other azacytidine analogs such as 5-azacytidine, 6-azacytidine (6-AzaC, Sigma-Chem.) and dihydroazacytidine (DHAC) did not act synergistically with cDDP or 4-HC.

SECTION HEADING: P Pharmacology

CLASSIF. CODE: 52 Chemotherapy - non-clinical
66 Drug Interactions

CONTROLLED TERM:
IN-VITRO *FT; CYTOSTATIC *FT; **COMB.** *FT; CYTOTOX. *FT; HEY-CELL *FT; MELANOMA *FT; NEOPLASM *FT; CARCINOMA *FT; NEOPLASM *FT; DRUG-COMPARISON *FT; ADENOCARCINOMA *FT; TUMOR-CELL *FT; TISSUE-CULTURE *FT
[01] DEOXYAZACYTIDINE *PH; DEOXYAZACYTIDINE *DI; PHARMACHEMIE *FT; CISPLATIN *DI; HYDROPEROXYCYCLOPHOSPHAMIDE *DI; CYTOSTATICS *FT; DEOXYAZAC *RN; PH *FT; DI *FT
[02] CISPLATIN *PH; CISPLATIN *DI; DEOXYAZACYTIDINE *DI; AZACYTIDINE *DI; AZACYTIDINE-6 *DI; DIHYDROAZACYTIDINE-5 *DI; SIGMA-CHEM. *FT; CYTOSTATICS *FT; CISPLATIN *RN; PH *FT; DI *FT
[03] HYDROPEROXYCYCLOPHOSPHAMIDE *PH; HYDROPEROXYCYCLOPHOSPHAMIDE *DI; DEOXYAZACYTIDINE *DI; AZACYTIDINE *DI; AZACYTIDINE-6 *DI; DIHYDROAZACYTIDINE-5 *DI; SIGMA-CHEM. *FT; CYTOSTATICS *FT; HOOCYCLOP *RN; PH *FT; DI *FT
[04] AZACYTIDINE *PH; AZACYTIDINE *DI; CISPLATIN *DI; HYDROPEROXYCYCLOPHOSPHAMIDE *DI; ANTIBIOTICS *FT; CYTOSTATICS *FT; AZACYTIDI *RN; PH *FT; DI *FT
[05] AZACYTIDINE-6 *DI; SIGMA-CHEM. *FT; CISPLATIN *DI; HYDROPEROXYCYCLOPHOSPHAMIDE *DI; CYTOSTATICS *FT; AZACYTID6 *RN; DI *FT
[06] DIHYDROAZACYTIDINE-5 *DI; CISPLATIN *DI; HYDROPEROXYCYCLOPHOSPHAMIDE *DI; CYTOSTATICS *FT; DIHAZACY5 *RN; DI *FT
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L116 ANSWER 31 OF 49 EMBASE
on STN DUPLICATE 4
ACCESSION NUMBER: 2004150082 EMBASE
TITLE: Growth-inhibitory effect of a novel synthetic triterpenoid, 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid, on ovarian carcinoma cell lines not dependent on peroxisome proliferator-activated receptor-.gamma. expression.
AUTHOR: Melichar B.; Konopleva M.; Hu W.; Melicharova K.; Andreeff M.; Freedman R.S.
CORPORATE SOURCE: R.S. Freedman, Department of Gynecologic Oncology, University of Texas, M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, United States. rfreedma@mdanderson.org
SOURCE: Gynecologic Oncology, (2004) 93/1 (149-154).
Refs: 23

ISSN: 0090-8258 CODEN: GYNOA3
PUBLISHER IDENT.: S 0090-8258(04)00012-5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 010 Obstetrics and Gynecology
016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
Objectives. Despite the advent of new chemotherapeutic drugs in recent decades, epithelial ovarian carcinoma (EOC) remains the leading cause of death from gynecologic cancers, and new therapeutic targets and agents are urgently needed. 2-Cyano-3,12-dioxoolean-1,9-dien-28-oic acid (**CDDO**) is a novel synthetic triterpenoid with anti-tumor activity against a wide range of tumors in vitro and in vivo. **CDDO** is a ligand for the peroxisome proliferator- activated receptor-.gamma. (PPAR.gamma.). The aim of the present study was to evaluate **CDDO** activity in EOC cell lines in vitro.
Methods. The expression of PPAR.gamma. was examined by real-time quantitative reverse transcription polymerase chain reaction (RT-PCR) in eight EOC cell lines (2774, SKOV3, CAOV3, OVCAR3, NMP-1, HEY, 2008 and 2008.C13), and the growth inhibitory activity of **CDDO** was assessed using the MTT assay.
Results. PPAR.gamma. RNA was expressed in all eight cell lines examined, but the expression varied widely among cell lines. In contrast, **CDDO** showed a similar degree of activity in different EOC cell lines independent of cisplatin sensitivity, with 50% inhibitory concentrations ranging from 1 to 4 .mu.M. Experiments combining **CDDO** with cisplatin and paclitaxel indicated weak antagonism. The growth-inhibitory activity of **CDDO** was unaffected by PPAR.gamma. antagonist T007. Conclusions. Although differences were observed in PPAR.gamma. expression in EOC cell lines, **CDDO** had similar growth-inhibitory activity in all cell lines examined, indicating that the antitumor activity of **CDDO** in vitro is mediated by a mechanism independent of PPAR.gamma.. The activity of **CDDO** in platinum-resistant cell lines is encouraging with respect to the potential clinical use of the drug.

CONTROLLED TERM: Medical Descriptors:
*cancer inhibition
*ovary carcinoma
*cancer cell culture
drug activity
protein expression
real time polymerase chain reaction
nitroblue tetrazolium test
drug sensitivity
gene expression
human
controlled study
human cell
article
priority journal
Drug Descriptors:
***2 cyano 3,12 dioxoolean 1,9 dien 28 oic acid: CB, drug combination**
*2 cyano 3,12 dioxoolean 1,9 dien 28 oic acid: DV, drug development
*2 cyano 3,12 dioxoolean 1,9 dien 28 oic acid: PD, pharmacology
***1,3 dioxolane derivative: CB, drug combination**
*1,3 dioxolane derivative: DV, drug development
*1,3 dioxolane derivative: PD, pharmacology

***triterpenoid: CB, drug combination**
*triterpenoid: DV, drug development
*triterpenoid: PD, pharmacology
*peroxisome proliferator activated receptor gamma: EC, endogenous compound
cisplatin: CB, drug combination
cisplatin: PD, pharmacology
paclitaxel: CB, drug combination
paclitaxel: PD, pharmacology
messenger RNA: EC, endogenous compound
unclassified drug

CAS REGISTRY NO.: (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (paclitaxel) 33069-62-4
COMPANY NAME: National Cancer Institute (United States); Bristol Myers Squibb (United States)

L116 ANSWER 32 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003285614 EMBASE
TITLE: The novel synthetic triterpenoid, **CDDO** -imidazolide, inhibits inflammatory response and tumor growth in vivo.
AUTHOR: Place A.E.; Suh N.; Williams C.R.; Risingsong R.; Honda T.; Honda Y.; Gribble G.W.; Leesnitzer L.M.; Stimmel J.B.; Willson T.M.; Rosen E.; Sporn M.B.
CORPORATE SOURCE: M.B. Sporn, Department of Pharmacology, Dartmouth Medical School, Remsen 524, Hanover, NH 03755, United States
SOURCE: Clinical Cancer Research, (1 Jul 2003) 9/7 (2798-2806). Refs: 53
ISSN: 1078-0432 CODEN: CCREF4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
1[2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (**CDDO**-Im) is a novel synthetic triterpenoid more potent than its parent compound, 2-cyano-3,12 -dioxooleana-1,9(11)-dien-28-oic acid (**CDDO**), both in vitro and in vivo. **CDDO**-Im is highly active in suppressing cellular proliferation of human leukemia and breast cancer cell lines (IC(50), .apprx.10-30 .mu.M). In U937 leukemia cells, **CDDO**-Im also induces monocytic differentiation as measured by increased cell surface expression of CD11b and CD36. In each of these assays, **CDDO**-Im is several-fold more active than **CDDO**. Although **CDDO** and **CDDO**-Im both bind and transactivate peroxisome proliferator-activated receptor (PPAR) .gamma., the irreversible PPAR.gamma. antagonist GW9662 does not block the ability of either **CDDO** or **CDDO**-Im to induce differentiation; moreover, PPAR.gamma.-null fibroblasts are still sensitive to the growth-suppressive effects of **CDDO**. Thus, **CDDO**-Im has significant actions independent of PPAR.gamma. transactivation. In addition, the rexinoid LG100268 and the deltanoid ILX23-7553 (ILX7553) synergize with ***CDDO*** and **CDDO**-Im to induce differentiation. In vivo, ***CDDO*** -Im is a potent inhibitor of de novo inducible nitric oxide synthase expression in primary mouse macrophages. Moreover, **CDDO**-Im inhibits growth of B16 murine melanoma and L1210 murine leukemia cells in vivo. The potent effects of **CDDO**-Im, both in vitro and in vivo, suggest it should be considered for clinical use.

CONTROLLED TERM: Medical Descriptors:

*cancer inhibition
*tumor growth
cell proliferation
cancer cell culture
IC 50
leukemia cell
cell differentiation
measurement
cell surface
antigen expression
cell assay
antineoplastic activity
null allele
fibroblast
growth inhibition
drug potentiation
protein expression
melanoma cell
drug effect
nonhuman
male
female
mouse
animal experiment
animal model
controlled study
animal cell
article
priority journal
Drug Descriptors:
*1 [2 cyano 3,12 dioxooleana 1,9(11) dien 28 oyl]imidazole: PD, pharmacology
*imidazole derivative: PD, pharmacology
triterpenoid
peroxisome proliferator activated receptor gamma: EC, endogenous compound
gw 9662: PD, pharmacology
receptor blocking agent: PD, pharmacology
6 [1 (5,6,7,8 tetrahydro 3,5,5,8,8 pentamethyl 2 naphthyl)cyclopropyl]nicotinic acid: PD, pharmacology
ilx 7553: PD, pharmacology
vitamin D derivative: PD, pharmacology
unclassified drug

CAS REGISTRY NO.: (6 [1 (5,6,7,8 tetrahydro 3,5,5,8,8 pentamethyl 2 naphthyl)cyclopropyl]nicotinic acid) 153559-76-3
CHEMICAL NAME: (1) Lg 100268; (2) Ilx 7553; Gw 9662
COMPANY NAME: (1) Ligand Pharmaceuticals (United States); (2) Ilex Oncology (United States)

L116 ANSWER 33 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1999434475 EMBASE
TITLE: Novel synthetic oleanane triterpenoids: A series of highly active inhibitors of nitric oxide production in mouse macrophages.
AUTHOR: Honda T.; Rounds B.A.V.; Bore L.; Favaloro F.G. Jr.; Gribble G.W.; Suh N.; Wang Y.; Sporn M.B.
CORPORATE SOURCE: G.W. Gribble, Department of Chemistry, Dartmouth College, Hanover, NH 03755, United States
SOURCE: Bioorganic and Medicinal Chemistry Letters, (20 Dec 1999) 9/24 (3429-3434).
Refs: 16

ISSN: 0960-894X CODEN: BMCLE8
PUBLISHER IDENT.: S 0960-894X(99)00623-X
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
Novel oleanane triterpenoids with modified rings A and C were designed and synthesized. Among them, methyl 2-carboxy-3,12-dioxooleana-1,9-dien-28-oate showed similar high inhibitory activity (IC50 = 0.8 nM) to 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (**CDDO**), which we have synthesized previously, against production of nitric oxide induced by interferon-.gamma. in mouse macrophages.

CONTROLLED TERM: Medical Descriptors:
nonhuman
mouse
animal cell
chemical modification
structure activity relation
partial drug synthesis
macrophage
drug inhibition
article
Drug Descriptors:
*nitric oxide
*methyl 2 carboxy 3,12 dioxooleana 1,9 dien 28 oate: DV, drug development
*methyl 2 carboxy 3,12 dioxooleana 1,9 dien 28 oate: AN, drug analysis
*methyl 2 carboxy 3,12 dioxooleana 1,9 dien 28 oate: PD, pharmacology
*oleanane triterpenoid: DV, drug development
*oleanane triterpenoid: AN, drug analysis
*oleanane triterpenoid: PD, pharmacology
*triterpenoid: DV, drug development
*triterpenoid: AN, drug analysis
*triterpenoid: PD, pharmacology
*drug analog: DV, drug development
*drug analog: AN, drug analysis
*drug analog: PD, pharmacology
CAS REGISTRY NO.: (Nitric Oxide) 10102-43-9

L116 ANSWER 34 OF 49 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 1998367502 EMBASE
TITLE: Design and synthesis of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid, a novel and highly active inhibitor of nitric oxide production in mouse macrophages.
AUTHOR: Honda T.; Rounds B.A.V.; Gribble G.W.; Suh N.; Wang Y.; Sporn M.B.
CORPORATE SOURCE: G.W. Gribble, Department of Chemistry, Dartmouth College, Hanover, NH 03755, United States
SOURCE: Bioorganic and Medicinal Chemistry Letters, (6 Oct 1998) 8/19 (2711-2714).
Refs: 13
ISSN: 0960-894X CODEN: BMCLE8
PUBLISHER IDENT.: S 0960-894X(98)00479-X
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry

030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
New derivatives with electron-withdrawing substituents at the C-2 position of 3-oxoolean-1-en-28-oic acid were synthesized. Among them, 2-cyano-3,12-dioxoleam-1,9-dien-28-oic acid (**CDDO**) was 400 times more potent than previous compounds we have made as an inhibitor of production of nitric oxide induced by interferon .gamma. in mouse macrophages (IC50, 0.4 nM). The potency of **CDDO** was similar to that of dexamethasone, although ***CDDO*** does not act through the glucocorticoid receptor.

CONTROLLED TERM: Medical Descriptors:
*drug synthesis
macrophage
drug structure
drug inhibition
drug potency
structure activity relation
nonhuman
mouse
animal cell
article
Drug Descriptors:
*nitric oxide
*nitric oxide synthase inhibitor: AN, drug analysis
*nitric oxide synthase inhibitor: CM, drug comparison
*nitric oxide synthase inhibitor: DV, drug development
*2 cyano 3,12 dioxoolean 1,9 dien 28 oic acid: AN, drug analysis
*2 cyano 3,12 dioxoolean 1,9 dien 28 oic acid: CM, drug comparison
*2 cyano 3,12 dioxoolean 1,9 dien 28 oic acid: DV, drug development
gamma interferon
dexamethasone: CM, drug comparison
dexamethasone: IT, drug interaction
glucocorticoid antagonist: IT, drug interaction
mifepristone: IT, drug interaction
unclassified drug
CAS REGISTRY NO.: (nitric oxide) 10102-43-9; (gamma interferon) 82115-62-6; (dexamethasone) 50-02-2; (mifepristone) 84371-65-3
CHEMICAL NAME: Ru 486

L116 ANSWER 35 OF 49 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:503873 BIOSIS
DOCUMENT NUMBER: PREV200300499193
TITLE: Synthetic triterpenoids suppress inflammation in the gastrointestinal tract: mechanisms of **interaction** of **CDDO** and **CDDO**-Imidazolide with interferon-gamma, TGF-beta, and Smad signaling.
AUTHOR(S): Heiss, Elke H. [Reprint Author]; Minns, Laurie A.; Suh, Nanjoo; Buzoni-Gatel, Dominique; Kasper, Lloyd H.; Gribble, Gordon W.; Honda, Tadashi; Sporn, Michael B.
CORPORATE SOURCE: Department of Pharmacology, Dartmouth Medical School, Hanover, NH, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 1348. print. Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.

ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Oct 2003
Last Updated on STN: 29 Oct 2003
CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Digestive system - Physiology and biochemistry 14004
Digestive system - Pathology 14006
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Endocrine - General 17002
Pharmacology - General 22002
Pharmacology - Connective tissue, bone and collagen-acting drugs 22012
Pharmacology - Digestive system 22014
Pharmacology - Immunological processes and allergy 22018
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508
Immunology, parasitological 35000
Medical and clinical microbiology - General and methods 36001
Chemotherapy - General, methods and metabolism 38502
Chemotherapy - Antiparasitic agents 38510
Parasitology - General 60502
Invertebrata: comparative, experimental morphology, physiology and pathology - Protozoa 64002
INDEX TERMS: Major Concepts
Digestive System (Ingestion and Assimilation); Immune System (Chemical Coordination and Homeostasis); Parasitology; Pharmacology
INDEX TERMS: Parts, Structures, & Systems of Organisms
fibroblast; gastrointestinal tract: digestive system; intestine: digestive system; macrophage: blood and lymphatics, immune system
INDEX TERMS: Diseases
Toxoplasma gondii cyst: infectious disease, parasitic disease
INDEX TERMS: Diseases
gastrointestinal tract cancer: digestive system disease, neoplastic disease, prevention and control
Gastrointestinal Neoplasms (MeSH)
INDEX TERMS: Diseases
gastrointestinal tract inflammation: digestive system disease, immune system disease, drug therapy
INDEX TERMS: Diseases
inflammatory bowel disease: digestive system disease, immune system disease, drug therapy
Inflammatory Bowel Diseases (MeSH)
INDEX TERMS: Chemicals & Biochemicals
CDD0: antiinfective-drug, antiinflammatory-drug,

antineoplastic-drug, antiparasitic-drug, gastrointestinal-drug, immunologic-drug, intraperitoneal administration, pharmacodynamics, synthetic triterpenoid; CDDO-imidazolide: antiinflammatory-drug, antineoplastic-drug, gastrointestinal-drug, immunologic-drug, synthetic triterpenoid; Smad7: regulation, signaling; Smad7 mRNA [Smad7 messenger RNA]: regulation, signaling; TGF-beta-1 [transforming growth factor-beta-1]: regulation, signaling; inducible nitric oxide synthase [iNOS] [EC 1.14.13.39]: regulation, synthesis; interferon-gamma [IFN-gamma]: regulation, signaling, synthesis; interferon-gamma mRNA [interferon-gamma messenger RNA]: regulation; nitric oxide; tumor necrosis factor [TNF]: regulation, synthesis; tumor necrosis factor mRNA [tumor necrosis factor messenger RNA]: regulation

ORGANISM: Classifier
Sporozoa 35400
Super Taxa
Protozoa; Invertebrata; Animalia
Organism Name
Toxoplasma gondii (species): parasite
Taxa Notes
Animals, Invertebrates, Microorganisms, Protozoans

REGISTRY NUMBER: 501433-35-8 (inducible nitric oxide synthase)
125978-95-2 (inducible nitric oxide synthase)
501433-35-8 (iNOS)
125978-95-2 (iNOS)
501433-35-8 (EC 1.14.13.39)
125978-95-2 (EC 1.14.13.39)
10102-43-9 (nitric oxide)

L116 ANSWER 36 OF 49 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2004:165951 BIOSIS
DOCUMENT NUMBER: PREV200400161124
TITLE: Bortezomib/proteasome inhibitor PS-341 and triterpenoid **CDDO**-Im induce **synergistic** apoptosis in multiple myeloma (MM) cells.
AUTHOR(S): Chauhan, Dharminder [Reprint Author]; Li, Guilan [Reprint Author]; Hideshima, Teru [Reprint Author]; Podar, Klaus [Reprint Author]; Catley, Laurence [Reprint Author]; Munshi, Nikhil [Reprint Author]; Sporn, Michael B.; Anderson, Kenneth C. [Reprint Author]
CORPORATE SOURCE: Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 935a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Mar 2004
Last Updated on STN: 24 Mar 2004
ABSTRACT:The synthetic triterpenoid 2-cyano-3, 12-dioxoolean-1, 9-dien-28-oic acid (**CDDO**) induce apoptosis in various leukemic cells. Here we show that **CDDO** and its new derivative **CDDO**-Imidazolide (***CDDO*** -Im) trigger apoptosis in multiple myeloma (MM) cells resistant to conventional therapies including **melphalan**, **doxorubicin**,

and dexamethasone (Dex) without affecting the viability of normal cells. ***CDDO*** -Im induces apoptosis in MM cells obtained from patients refractory to Dex and thalidomide. Moreover, **CDDO**-Im inhibits the paracrine growth of MM cells co-cultured with patient bone marrow (BM) stromal cells and overcomes interleukin-6-mediated protection against Dexamethasone. The ***CDDO*** -Im-triggered apoptosis is associated with activation of caspase-8/9 and is blocked in the presence of caspase-3 inhibitor. Importantly, **CDDO**-Im and Bortezomib/proteasome inhibitor PS-341 trigger a **synergistic** apoptotic effect in MM cells. Together, these findings provide the framework for clinical evaluation of triterpenoids, either alone or in combination with Bortezomib, to overcome drug resistance and improve outcome in MM.

CONCEPT CODE:
General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Cytology - Human 02508
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508

INDEX TERMS:
Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Hematology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Pharmacology

INDEX TERMS:
Parts, Structures, & Systems of Organisms
bone marrow stromal cell: blood and lymphatics, immune system; plasma cell: blood and lymphatics, immune system

INDEX TERMS:
Diseases
multiple myeloma: blood and lymphatic disease, immune system disease, neoplastic disease
Multiple Myeloma (MeSH)

INDEX TERMS:
Chemicals & Biochemicals
2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid-imidazole [**CDDO**-Im]: antineoplastic-drug; PS-341: antineoplastic-drug, enzyme inhibitor-drug; bortezomib; caspase-3; caspase-8; dexamethasone: antineoplastic-drug; **doxorubicin**: antineoplastic-drug; interleukin-6; **melphalan**: antineoplastic-drug; proteasome [EC 3.4.25.1]

INDEX TERMS:
Miscellaneous Descriptors
drug **synergy**

ORGANISM:
Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common): patient

Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
REGISTRY NUMBER: 31692-79-2Q (PS-341)
179324-69-7Q (PS-341)
179324-69-7 (bortezomib)
169592-56-7 (caspase-3)
179241-78-2 (caspase-8)
50-02-2 (dexamethasone)
23214-92-8 (**doxorubicin**)
148-82-3 (**melphalan**)
140879-24-9 (proteasome)
140879-24-9 (EC 3.4.25.1)

L116 ANSWER 37 OF 49 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:475455 BIOSIS
DOCUMENT NUMBER: PREV200300475455
TITLE: The coordinate regulation, physical **interaction**, and functional association of UBE1L and ISG15 during retinoid induction of acute promyelocytic differentiation.
AUTHOR(S): Pitha-Rowe, Ian [Reprint Author]; Kitareewan, Sutisak; Freemantle, Sarah; Hassel, Bret; Dmitrovsky, Ethan
CORPORATE SOURCE: Department of Pharmacology, Dartmouth Medical School, Hanover, NH, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 843. print.
Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Oct 2003
Last Updated on STN: 15 Oct 2003
CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Lipids 10066
INDEX TERMS: Major Concepts
Biochemistry and Molecular Biophysics
INDEX TERMS: Parts, Structures, & Systems of Organisms
acute promyelocytic cell
INDEX TERMS: Chemicals & Biochemicals
4-HPR; 9-cis retinoic acid; **CDDO**; ISG15: expression, regulation; PML/RAR-alpha: degradation; RNA: small inhibitory; UBE1L: regulation; interferon; retinoic acid; retinoid; roziglitazone
INDEX TERMS: Miscellaneous Descriptors
physical **interaction**
REGISTRY NUMBER: 5300-03-8 (9-cis retinoic acid)
302-79-4 (retinoic acid)

L116 ANSWER 38 OF 49 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2004:150197 BIOSIS
DOCUMENT NUMBER: PREV200400146889
TITLE: The triterpenoid **CDDO**-imidazolide induces apoptosis of CLL B-cells, through a **Bcl-2**

-independent mechanism and **synergizes** with fludarabine.

AUTHOR(S): Pedersen, Irene M. [Reprint Author]; Zapata, Juan [Reprint Author]; Samuel, Temesgen [Reprint Author]; Scott, Fiona [Reprint Author]; Sporn, Michael; Kipps, Thomas J.; Salvesen, Guy [Reprint Author]; Reed, John C. [Reprint Author]

CORPORATE SOURCE: Burnham Institute, La Jolla, CA, USA

SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 431a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)

LANGUAGE: English

ENTRY DATE: Entered STN: 17 Mar 2004
Last Updated on STN: 17 Mar 2004

ABSTRACT:Chronic Lymphocytic **Leukemia** (CLL) is currently considered an incurable disease. This is in part the result of the selection over time of CLL subclones that develop resistance to standard **chemotherapeutic** drugs. Therefore there is a need for new agents that can overcome the chemoresistance of CLL cells that often increase in the course of this disease, mandating development of novel agents for the treatment of this disease. Triterpenoids represent a class of naturally occurring compounds and synthetic derivatives with demonstrated anti-**tumor** activity and low toxicity in animal xenograft models. We compared the effect of the synthetic triterpenoid 2-Cyano-3, 12-Dioxooleana-1,9-Dien-28-Oic Acid (**CDDO**) with its imidazolide derivative (**CDDO**-Im) on human CLL B-cells and mouse splenocytes from a mouse transgenic model of SLL/CLL (over-expressing ***Bcl*** -**2** and a version of TRAF2). **CDDO**-Im showed 5 to 10 fold stronger apoptosis-inducing activity than **CDDO** and induced apoptosis in all (n=40) consecutively tested CLL samples, with an effective dose (IC50) of 350 nM or less. Transgenic, **neoplastic** cells showed chemo-resistance to conventional anti-**tumor** agents, such as fludarabine and dexamethazone, but similar to human CLL B-cells, transgenic B-cells demonstrated highly sensitivity to **CDDO**-Im. Both ***CDDO*** and **CDDO**-Im induced apoptosis through activation of Caspase-8. Accordingly, **CDDO**-Im-induced apoptosis could be blocked by CrmA, a Caspase-8 inhibitor, as well as by specific down-regulation of Caspase-8 expression using antisense oligonucleotides electroporated into the CLL B-cells. Examination of **CDDO**-Im effects on the expression of several apoptosis-relevant genes demonstrated that XIAP, an endogenous inhibitor of caspase-3, -7 and -9, was specifically down-regulated by ***CDDO*** -Im, but not by **CDDO**. In contrast, down-regulation of FLIP was induced by **CDDO**, but not by **CDDO**-Im. These results suggest that **CDDO** and **CDDO**-Im modulate different anti-**apoptotic** proteins in CLL B-cells and therefore have overlapping but district mechanisms of action. Furthermore **CDDO**-Im, but not ***CDDO*** works **synergistically** with with fludarabine monophosphate (Fludara) in inducing apoptosis of CLL B-cells, in vitro. These results indicate that triterpenoids, and particularly **CDDO**-Im, are able to overcome the apoptosis blockage induced by expression of high levels of anti-**apoptotic** proteins such as **Bcl**-**2**, whose up-regulation is a hallmark of many chemo-refractory **leukemias**, and underscore the potential of **CDDO**-Im for the treatment of refractory CLL patients either as a single anti-**tumor** agent or in combination with other conventional agents such as Fludarabine.

CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520

Cytology - Animal 02506
Cytology - Human 02508
Genetics - General 03502
Genetics - Animal 03506
Genetics - Human 03508
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508

INDEX TERMS: Major Concepts
Immune System (Chemical Coordination and Homeostasis); Molecular Genetics (Biochemistry and Molecular Biophysics); Pharmacology; **Tumor** Biology

INDEX TERMS: Parts, Structures, & Systems of Organisms
B cell: blood and lymphatics, immune system; lymphocyte: blood and lymphatics, immune system; splenocyte: blood and lymphatics, immune system

INDEX TERMS: Diseases
chronic lymphocytic **leukemia**: blood and lymphatic disease, immune system disease, **neoplastic** disease, drug therapy, CLL
Leukemia, Lymphocytic, Chronic (MeSH)

INDEX TERMS: Chemicals & Biochemicals
2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid [**CDDO**]: **antineoplastic**-drug;
2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid-imidazolide: **antineoplastic**-drug;
Bcl-2: expression; CrmA: enzyme inhibitor; TRAF2; XIAP [X-linked inhibitor of apoptosis]: endogenous, enzyme inhibitor; caspase-3: expression; caspase-7: expression; caspase-8: expression, regulation; caspase-9: expression; dexamethasone: **antineoplastic**-drug;
fludarabine: **antineoplastic**-drug

INDEX TERMS: Miscellaneous Descriptors
cell apoptosis; drug **synergy**

ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGANISM: Classifier

Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common): transgenic
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

REGISTRY NUMBER: 169592-56-7 (caspase-3)
189258-14-8 (caspase-7)
179241-78-2 (caspase-8)
180189-96-2 (caspase-9)
50-02-2 (dexamethasone)
21679-14-1 (fludarabine)

GENE NAME: human **Bcl-2** gene (Hominidae): expression, transgene; human TRAF2 gene (Hominidae): expression, transgene

L116 ANSWER 39 OF 49 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2002:630191 BIOSIS

DOCUMENT NUMBER: PREV200200630191

TITLE: Mechanisms of **synergistic interaction** between synthetic triterpenoids and transforming growth factor (TGF)-beta in anti-inflammation.

AUTHOR(S): Heiss, Elke [Reprint author]; Suh, Nanjoo; Boettinger, Erwin P.; Farris, M. Rendi; Place, Andrew E.; Sporn, Michael B.

CORPORATE SOURCE: Dartmouth Medical School, Hanover, NH, USA

SOURCE: Cancer Epidemiology Biomarkers and Prevention, (October, 2002) Vol. 11, No. 10 Part 2, pp. 1230s. print.
Meeting Info.: Proceedings of the American Association for Cancer Research Conference on Frontiers in Cancer Prevention Research. Boston, MA, USA. October 14-18, 2002. American Society of Preventive Oncology.
ISSN: 1055-9965.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 12 Dec 2002
Last Updated on STN: 12 Dec 2002

CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Cytology - Human 02508
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Endocrine - General 17002
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Pharmacology - Connective tissue, bone and collagen-acting drugs 22012
Pharmacology - Immunological processes and allergy 22018
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508

INDEX TERMS: Major Concepts
Enzymology (Biochemistry and Molecular Biophysics);

Immune System (Chemical Coordination and Homeostasis); Pharmacology; Tumor Biology

INDEX TERMS: Chemicals & Biochemicals
CDDO: antiinflammatory-drug, enzyme inhibitor-drug, immunologic-drug, triterpenoid; **CDDO**-Im: antiinflammatory-drug, enzyme inhibitor-drug, immunologic-drug, triterpenoid; IFN-gamma [interferon-gamma]; JAK; Smad 7; Stat1; TGF-beta [transforming growth factor-beta]; TNF-alpha [tumor necrosis factor-alpha]; cyclooxygenase-2 [COX-2]; nitric oxide synthase: inducible

INDEX TERMS: Miscellaneous Descriptors
intracellular signaling cascade; Meeting Abstract

ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
U4A/JAK cell line
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGANISM: Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
RelA cell line
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

REGISTRY NUMBER: 329900-75-6 (cyclooxygenase-2)
329900-75-6 (COX-2)
125978-95-2 (nitric oxide synthase)

L116 ANSWER 40 OF 49 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:335965 BIOSIS
DOCUMENT NUMBER: PREV200300335965
TITLE: Transgenic Mouse Models of Lymphoma for Preclinical Analysis of Novel Anti-**Cancer** Drugs.
AUTHOR(S): Pedersen, Irene M. [Reprint Author]; Zapata, Juan M.; Sporn, Michael; Carson, Dennis A.; Leoni, Lorenzo M.; Reed, John C.
CORPORATE SOURCE: The Burnham Institute, La Jolla, CA, USA
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 1365. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Jul 2003
Last Updated on STN: 23 Jul 2003

ABSTRACT:Collectively, low-grade non-Hodgkin's lymphomas represent the most common type of hematopoietic malignancy and rank among the most common ***neoplastic*** disorders worldwide. These disorders involve a slow expansion of mature **neoplastic** B-cells primarily as a result of reduced cell turnover due to failed programmed cell death, rather than because of increased rates of cell division. Traditional xenografts models, useful for

other **tumors** types, do not recapitulate the pathogenesis of these slow-growing **tumors**. Therefore, a need exists for pre-clinical animal models that can accurately simulate these low-grade malignancies. We have employed transgenic mouse models representative of low-grade follicular lymphoma (**Bcl-2** transgenic), mantle cell lymphoma (DELTAN-TRAF-2 transgenic. A kind gift from Dr. Choi Y., the Rockerfeller University, NY), and invasive (extranodal) lymphoma (**Bcl-2** /DELTAN-TRAF-2 double transgenic) for analysis of conventional and novel anticancer drugs. We used splenocytes isolated from these transgenic mice to test the anti-**tumor** activity of novel **chemotherapeutic** drugs, including the triterpenoid **CDDO** and its methyl-ester derivative (CDDOme), various retinoid/rexenoids, Indanocine (a tubulin polymerization inhibitor), the non-steroidal anti-inflammatory drug R-Etodolac (SDX-101), as well as conventional **chemotherapeutic** agents such as dexamethasone and fludarabine. **CDDO**, CDDOme, and R-Etodolac induced apoptosis of B-cells derived from all three models of lymphoma. In contrast, Fludarabine, Dexamethasone and Indanocine did not induce significant apoptosis in lymphoma cells, even at concentrations that were toxic for control splenic B cells from wild-type mice. In vivo analysis of **CDDO**, CDDOme, and R-Etodolac in these transgenic mouse models of low-grade lymphoma is currently underway. The data suggest that transgenic mouse models of low-grade lymphoma may be used for preclinical analysis of novel anti-**cancer** drugs.

CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - General 12502
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Pharmacology - General 22002
Pharmacology - Connective tissue, bone and collagen-acting drugs 22012
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Immunology - Immunopathology, tissue immunology 34508

INDEX TERMS: Major Concepts
Blood and Lymphatics (Transport and Circulation); Pharmacology; **Tumor** Biology

INDEX TERMS: Parts, Structures, & Systems of Organisms
splenic B cell: blood and lymphatics; splenocyte: blood and lymphatics

INDEX TERMS: Diseases
follicular lymphoma: blood and lymphatic disease, immune system disease, **neoplastic** disease, pathology
Lymphoma, Follicular (MeSH)

INDEX TERMS: Diseases
mantle cell lymphoma: blood and lymphatic disease, immune system disease, **neoplastic** disease, pathology
Lymphoma, Small Cleaved-Cell, Diffuse (MeSH)

INDEX TERMS: Chemicals & Biochemicals
Bcl-2: expression; **CDDO**: **antineoplastic**-drug; dexamethasone: antiinflammatory-drug; fludarabine:

antineoplastic-drug; indanocine:
antineoplastic-drug; racemic etodolac: enzyme inhibitor-drug

ORGANISM: Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common): transgenic
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

REGISTRY NUMBER: 50-02-2 (dexamethasone)
21679-14-1 (fludarabine)
265646-19-3 (indanocine)
41340-25-4 (racemic etodolac)

L116 ANSWER 41 OF 49 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:336888 BIOSIS
DOCUMENT NUMBER: PREV200300336888
TITLE: Chromatin-Mediated Transcriptional Activation with Novel Peroxisome Proliferator-Activated Receptor gamma(PPARgamma) Ligand 2-Cyano-3,12-dioxooleana-1,9-dien-28-oic Acid (**CDDO**) in Acute Promyelocytic Leukemia Cells.
AUTHOR(S): Tabe, Yoko [Reprint Author]; Konopleva, Marina [Reprint Author]; Tsao, Twee [Reprint Author]; Lapillonne, Helene [Reprint Author]; Jackson, C. Ellen [Reprint Author]; Andreeff, Michael [Reprint Author]
CORPORATE SOURCE: Blood and Marrow Transplantation, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 2191. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Jul 2003
Last Updated on STN: 23 Jul 2003

ABSTRACT:Acute promyelocytic leukemia (APL) is characterized by the oncogenic transcription factor PML-RARalpha that acts as a dominant negative transcriptional repressor through recruitment of histone deacetylase (HDAC). In addition, PML-RARalpha has been reported to repress the transactivation of peroxisome proliferator-activated receptor gamma (PPARgamma), a member of the ligand-activated nuclear receptor family, which recruits the p300/CBP coactivator with histone acetyltransferase activity. We have shown that PPARgamma is expressed in leukemic cells and that the PPARgamma ligand 2-Cyano-3,12-dioxooleana-1,9-dien-28-oic acid(**CDDO**) is a potent inducer of apoptosis and differentiation in leukemias(Blood 96(11):460a 2000). Here, we propose that **CDDO** induces transcriptional activation of RARbeta2 and p21WAF1 via histone modification in APL cells. First, we found that the induction of PML/RARalpha in U937/PR9 cells is associated with increased PPARgamma mRNA levels (p=0.027, quantitative TaqMan PCR) and enhanced sensitivity to **CDDO** (41% AnnexinV(+) in PML/RARalpha(+) vs. 12% in PML/RARalpha(-)). In NB4 cells, **CDDO** alone inhibited proliferation and induced apoptosis (IC50=0.3uM), and the **CDDO**/ATRA combination markedly enhanced differentiation, inhibited proliferation and induced apoptosis. In ATRA-resistant subclones (MR2, R4, and MR6; provided by Dr. W. Miller), **CDDO** induced apoptosis and increased differentiation when

combined with ATRA. Next, we investigated the effects of **CDDO** and ***CDDO*** /ATRA on RARbeta and p21WAF1 mRNA expression by TaqMan RT-PCR. In NB4 cells, **CDDO** induced RARbeta and p21WAF1 mRNA expression, and RARbeta was further enhanced by combination of **CDDO** with ATRA. In RA-resistant subclones, **CDDO** induced p21WAF1 mRNA, and **CDDO** /ATRA enhanced expression of RARbeta and p21WAF1. Then, we performed chromatin immunoprecipitation assays quantitated by TaqMan PCR to determine histone modifications, H3 lysine 9(H3-K9) acetylation and H3 lysine 4(H3-K4) methylation, which are known to correlate with open chromatin structure, transcription, and p300/CBP recruitment in RARbeta P2 and p21WAF1 promoter regions. In both, RARbeta P2 and p21WAF1 promoter regions, **CDDO** alone slightly increased H3-K9 acetylation and H3-K4 methylation (3-6 fold) with no effect on p300/CBP recruitment. **CDDO** markedly ***potentiated*** effects of ATRA in RARbeta P2 and p21WAF1, such as increase in H3-K9 acetylation (RARbeta P2, 177 fold by ATRA alone vs. 321 fold by ***CDDO*** /ATRA; p21WAF1, 3 fold vs. 17 fold), and increase in p300/CBP recruitment (RARbeta P2, 6 fold by ATRA vs. 18 fold by **CDDO**/ATRA; p21WAF1, 11 fold by ATRA vs. 60 fold by **CDDO**/ATRA). These results suggest that the PPARgamma ligand **CDDO** induces histone modifications in the RARbeta P2 and p21WAF1 promoter regions in APL cells. In combination with ATRA, **CDDO** induces maximal transcriptional activation by stimulating histone acetylation/methylation with recruitment of p300/CBP that overcomes the chromatin-mediated transcriptional repression in APL cells. This approach resulted in enhanced expression of RARbeta and p21WAF1 mRNA, in induction of differentiation and apoptosis in ATRA-resistant APL cells. Our data establish, for the first time, the paradigm of combined activation of RARalpha and PPARgamma as basis for "targeted transcription therapy" in APL.

CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508

INDEX TERMS: Major Concepts
Blood and Lymphatics (Transport and Circulation); Pharmacology; Tumor Biology

INDEX TERMS: Parts, Structures, & Systems of Organisms
acute promyelocytic leukemia cell: blood and lymphatics, immune system, apoptosis

INDEX TERMS: Diseases
acute promyelocytic leukemia: blood and lymphatic disease, neoplastic disease
Leukemia, Promyelocytic, Acute (MeSH)

INDEX TERMS: Chemicals & Biochemicals
2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid [peroxisome]: antineoplastic-drug, proliferator-activated receptor-gamma ligand; ATRA: antineoplastic-drug; H3 lysine 4; H3 lysine 9; RAR-alpha: activation; RAR-beta 2: p21-WAF 1, activation, expression; RAR-beta mRNA: expression; chromatin; p21-WAF 1 mRNA: expression; p300/CBP; proliferator-activated receptor-gamma;

proliferator-activated receptor-gamma mRNA
ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
NB4 cell line (cell line): human leukemia cells
U937/PR9 cell line (cell line): human monoblast cells/acute promyelocytic leukemia cells
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

L116 ANSWER 42 OF 49 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:261619 BIOSIS
DOCUMENT NUMBER: PREV200200261619
TITLE: A novel mechanism for reducing FLIP expression and sensitizing malignant cells to the TNF-family death ligand, **TRAIL**.
AUTHOR(S): Kim, Youngsoo [Reprint author]; Suh, Nanjoo; Sporn, Michael; Reed, John C. [Reprint author]
CORPORATE SOURCE: Burnham Institute, La Jolla, CA, USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 839a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 May 2002
Last Updated on STN: 1 May 2002
ABSTRACT:**TRAIL** (Apo2-ligand) is a member of the Tumor Necrosis Factor (TNF) family of cytokines which induces apoptosis. Because **TRAIL** preferentially kills tumor cells, sparing normal tissues, interest has emerged in applying this biological factor for cancer therapy in humans. However, not all tumors respond to **TRAIL**, particularly most hematopoietic malignancies, raising questions about resistance mechanisms. We demonstrate here that a variety of natural and synthetic ligands of PPARg sensitize cancer cell lines (including 9/11 solid tumors and 4/4 hematopoietic lines) and but not normal cells (bone marrow, peripheral blood lymphocytes, endothelial cells) to apoptosis induction by **TRAIL**. These PPARg ligands selectively reduce levels of FLIP, an apoptosis-suppressing protein which blocks early events in **TRAIL**/TNF-family death receptor signaling. PPARg ligands that displayed an ability to reduce FLIP expression and to sensitize tumor cell lines to **TRAIL** included naturally occurring prostanoids as well as synthethic thiazolinediones and triterpenoids, with the triterpenoids ***CDDO*** and **CDDO**-Me displaying the greatest potency. An excellent correlation was observed between the concentration of PPARg modulatory compounds required for reducing FLIP and sensitization to ***TRAIL*** -induced apoptosis. Furthermore, experiments in which FLIP expression was augmented by gene transfection or reduced by antisense oligonucleotides provided further evidence in support of an important role for FLIP in controlling the relative sensitivity of tumor lines to **TRAIL**. Interestingly, both PPARg agonists and antagonists displayed these effects on FLIP and **TRAIL**-sensitivity, regardless of the levels of PPARg expression and even in the presence of a PPARg dominant-negative mutant, indicating a PPARg-independent mechanism. Reductions in FLIP and sensitization to **TRAIL**-induced apoptosis were also not correlated with NF-kB, further suggesting a novel mechanism. PPARg modulatory compounds down-regulated FLIP by a post-transcriptional process, resulting in faster

degradation of the FLIP protein without a demonstrable change in FLIP mRNA levels. Furthermore, PPARg modulatory drugs induced increased ubiquitination of FLIP, both in intact cells and in cell extracts derived from drug-treated cells. Inhibitors of the 26s proteasome (MG132; lactacystin; epoximicin) prevented down-regulation of FLIP protein, in contrast to inhibitors of other types of proteases (caspases; calpains). Taken together, these findings demonstrate a new PPARg-independent mechanism of action for PPARg-binding drugs (thiazolinediones; triterpenoids), suggesting that these compounds have additional unknown targets which control a pathway for ubiquitination and degradation of anti-apoptotic protein, FLIP.

CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - Proteins, peptides and amino acids 10064
Endocrine - General 17002

INDEX TERMS: Major Concepts
Endocrine System (Chemical Coordination and Homeostasis)

INDEX TERMS: Chemicals & Biochemicals
FLIP: expression, regulation; FLIP mRNA [FLIP messenger RNA]; NF-kappa-B [nuclear factor-kappa-B]; PPARg ligand: mutation; **TRAIL**; antisense oligonucleotide; prostanoid; thiazolinedione; triterpenoid

INDEX TERMS: Miscellaneous Descriptors
Meeting Abstract

L116 ANSWER 43 OF 49 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:250092 BIOSIS
DOCUMENT NUMBER: PREV200200250092
TITLE: Effects of triterpenoid **CDDO** on the sensitivity to apoptosis in chronic lymphocytic leukemia.
AUTHOR(S): Pedersen, Irene M. [Reprint author]; Kitada, Shinichi [Reprint author]; Kim, Youngsoo [Reprint author]; Kipps, Thomas J.; Sporn, Michael; Suh, Nanjoo; Reed, John C. [Reprint author]
CORPORATE SOURCE: Burnham Institute, La Jolla, CA, USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 731a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Apr 2002
Last Updated on STN: 24 Apr 2002

ABSTRACT:Chronic lymphocytic leukemia (CLL) is characterized by an accumulation of CD5/CD19/CD23 small, mature lymphocytes, caused primarily by defects in apoptosis regulation rather than cell proliferation. Methods for increasing the sensitivity of leukemia cells to apoptosis could have therapeutic benefit. PPAR-gamma is a member of the retinoid/steroid family of ligand-dependent transcription factors that has been implicated in the expression of several apoptosis-regulating genes. Triterpenoids represent a class of naturally occurring and synthetic compounds with demonstrated anti-tumor activity. Some of these agents modulate PPAR-gamma activity, including **CDDO** (2-Cyano-3,12-Dioxoolean-1,9-Dien-28-Oic Acid) which functions at least in part as a weak PPAR-gamma agonist and CDDOm which is a PPAR-gamma antagonist. Because CLL cells generally express high levels of PPAR-gamma, we examined the effects of the triterpenoid compounds **CDDO** and CDDOm on freshly isolated CLL cells with respect to apoptosis and expression of apoptosis-regulatory genes. CLL cells in 12 of 12 patient samples were induced to undergo apoptosis in vitro when cultured with **CDDO**. Apoptosis

induced by **CDDO** was dose-dependent, with a mean effective dose for 50% killing (ED50) of 1uM (n=12). CDDOm was significantly less effective in inducing leukemia-cell apoptosis (p<0.021). However, classical thiazolidinedione-type PPAR-gamma agonists had only weak pro-apoptotic activity in cultured B-CLL cells. Examination of the effects of **CDDO** on expression of several apoptosis-relevant genes demonstrated significant reductions in the levels of c-FLIP, an antagonist of apoptosis induction by TNF-family death receptors such as Fas and the **TRAIL** receptors, DR4 and DR5. **CDDO**-mediated reductions in FLIP expression were observed in 11 out of 11 CLL samples tested and were demonstrable at concentrations of 1uM or less. Experiments in which CLL cells were treated with the combination of **CDDO** and recombinant **TRAIL** indicated that **CDDO** could sensitize CLL cells to apoptosis induced by this TNF-family death ligand. To explore the role of FLIP in CLL resistance to **TRAIL**-induced apoptosis, we introduced FLIP anti-sense (AS) oligonucleotides into CLL cells using electroporation. This resulted in complete ablation of leukemia-cell expression of FLIP protein, determined by immunoblot analysis. Antisense-mediated inhibition of FLIP expression sensitized the B-CLL cells to ***TRAIL*** -induced apoptosis, whereas control oligonucleotides had no effect. These data suggest that the synthetic triterpenoid **CDDO** should be explored for the treatment of CLL, either alone or in combination with other immune-based anti-cancer therapies.

CONCEPT CODE:
General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Cytology - Human 02508
Biochemistry studies - Proteins, peptides and amino acids 10064
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Endocrine - General 17002
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508

INDEX TERMS: Major Concepts
Blood and Lymphatics (Transport and Circulation); Immune System (Chemical Coordination and Homeostasis); Tumor Biology

INDEX TERMS: Parts, Structures, & Systems of Organisms
lymphocyte: blood and lymphatics, immune system, apoptosis

INDEX TERMS: Diseases
chronic lymphocytic leukemia: blood and lymphatic disease, immune system disease, neoplastic disease
Leukemia, Lymphocytic, Chronic (MeSH)

INDEX TERMS: Chemicals & Biochemicals
CDDO: expression, triterpenoid; DR4: Fas receptor; DR5: **TRAIL** receptor; TNF [tumor necrosis factor]; apoptosis-relevant gene; c-FLIP: expression

INDEX TERMS: Miscellaneous Descriptors
Meeting Abstract

ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name

human: patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

L116 ANSWER 44 OF 49 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:129933 BIOSIS
DOCUMENT NUMBER: PREV200200129933
TITLE: Triterpenoids **CDDO** and **CDDO**-Me down-regulate FLIP expression and sensitize AML cells to **TRAIL**-induced apoptosis.
AUTHOR(S): Suh, Won-Suk [Reprint author]; Shinichi, Kitada [Reprint author]; Kim, Youngsoo [Reprint author]; Andreeff, Michael; Sporn, Michael; Suh, Nanjoo; Reed, John C. [Reprint author]
CORPORATE SOURCE: Burnham Institute, La Jolla, CA, USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 118a-119a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Feb 2002
Last Updated on STN: 26 Feb 2002

ABSTRACT:Though often exhibiting initial responses to **chemotherapy**, Acute Myelogenous **Leukemia** (AML) remains a deadly disease for most adult patients, due primarily to the emergence of chemoresistant cells. Defects in apoptosis pathways make important contributions to chemoresistance, suggesting a need to restore apoptosis sensitivity in AML or to identify alternative pathways for apoptosis induction. Triterpenoids represent a class of naturally occurring and synthetic compounds with demonstrated anti-***tumor*** activity. Some of these agents modulate PPARg activity, including **CDDO** (2-Cyano-3,12-Dioxoolean-1,9-Dien-28-Oic Acid) and its methyl ester (**CDDO**-Me), which function as weak agonists and antagonists of PPARg, respectively. Because PPARg has been linked to regulation of apoptosis-relevant genes, we explored the effects of the triterpenoid compounds **CDDO** and **CDDO**-Me on established AML cell lines (HL-60; U937; AML-2) and on freshly isolated AML blasts with respect to apoptosis and expression of apoptosis-regulatory genes. When used individually, **CDDO** and **CDDO**-Me reduced the viability of all AML lines tested in a dose-dependent manner, with effective doses for killing 50% of cells (ED50) in 48 hrs of apprx1 uM and 0.5 uM, respectively. This loss of cell viability was attributed to apoptosis, based characteristic cell morphology and on evidence of caspase activation. Immunoblot analysis demonstrated evidence of activation of caspases-3, 7, and 8, but not 9, suggesting involvement of the "extrinsic" pathway, which has been linked to apoptosis induction by TNF-family death receptors. Accordingly, **CDDO** and **CDDO**-Me induced rapid reductions in the levels of FLIP protein, an endogenous antagonist of caspase-8 activation, without altering the levels of several other apoptosis-relevant proteins, including FADD, DR4, DR5, ***Bcl*** **-2**, Bcl-XL, Mcl-1, Bax, and others. Reductions in FLIP were detectable within 3 hrs after exposure of AML cell lines to **CDDO** or **CDDO**-Me, with essentially complete loss of FLIP protein expression within 6-9 hrs. The drug-induced decline in FLIP levels was dose-dependent over the concentration range of 0.1-1 uM, with partial reductions evident at 0.1 uM and >95% reduction in FLIP proteins attained with 0.5 uM or less of these compounds. **CDDO**- and **CDDO**-Me-induced reductions in FLIP protein were not secondary to caspase activation, as determined by experiments using the broad-spectrum caspase inhibitor, zVAD-fmk. FLIP

reductions also preceded caspase processing in time-course experiments, using AML cell lines treated with **CDDO** and **CDDO**-Me. When used at doses that resulted in little apoptosis (0.3 uM), **CDDO** and ***CDDO*** -Me down-regulated FLIP and rendered AML cell lines sensitive to ***TRAIL*** , a TNF-family death ligand. In contrast, **TRAIL** alone failed to induce apoptosis of AML cell lines. Similar results were obtained using freshly isolated AML blasts. In contrast, apoptosis of peripheral blood lymphocytes and normal bone marrow cells was not triggered by **CDDO**, ***CDDO*** -Me, **TRAIL**, or combinations of these agents. The findings suggest that triterpenoids warrant investigation in the treatment of AML, alone or in combination with **TRAIL** or other immune-based therapies.

CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Cytology - Human 02508
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508

INDEX TERMS: Major Concepts
Blood and Lymphatics (Transport and Circulation); Immune System (Chemical Coordination and Homeostasis); Pharmacology; **Tumor** Biology

INDEX TERMS: Parts, Structures, & Systems of Organisms
myeloblast: blood and lymphatics, immune system

INDEX TERMS: Chemicals & Biochemicals
CDDO: **antineoplastic**-drug; **CDDO**-methyl ester: **antineoplastic** -drug; FLIP protein: expression, regulation; **TRAIL** [**tumor** necrosis factor-related apoptosis inducing ligand]; apoptosis regulatory gene; caspase-3: activation; caspase-7: activation; caspase-8: activation; zVAD-fmk: enzyme inhibitor-drug

INDEX TERMS: Miscellaneous Descriptors
Meeting Abstract; Meeting Poster

ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
AML-2 cell line: apoptosis, human acute myelogenous **leukemia** cell, viability
HL-60 cell line: apoptosis, human acute myelogenous **leukemia** cell, viability
U937 cell line: apoptosis, human acute myelogenous **leukemia** cell, viability
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

REGISTRY NUMBER: 169592-56-7 (caspase-3)
189258-14-8 (caspase-7)
179241-78-2 (caspase-8)

Searched by Barb O'Bryen, STIC 571-272-2518

187389-52-2 (ZVAD-FMK)

L116 ANSWER 45 OF 49 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:300204 BIOSIS
DOCUMENT NUMBER: PREV200100300204
TITLE: Novel synthetic triterpenoid **CDDO**-Me: Potent antiproliferative, proapoptotic and differentiating agent in AML.
AUTHOR(S): Konopleva, Marina [Reprint author]; Stiouf, Irina [Reprint author]; Estrov, Zeev; Tsao, Twee [Reprint author]; Harris, David; Munsell, Mark; Leysath, Clinton [Reprint author]; Zhao, Shourong [Reprint author]; Jackson, C. Ellen [Reprint author]; Chang, Shi-rong [Reprint author]; Sporn, Michael; Andreeff, Michael [Reprint author]
CORPORATE SOURCE: Molecular Hematology and Therapy, University of Texas M. D. Anderson Cancer Center, Houston, TX, USA
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 121a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Jun 2001
Last Updated on STN: 19 Feb 2002

ABSTRACT:We report the effects the of C-28 methyl ester of 2-cyano-3, 12-dioxoolean-1, 9-dien-28-oic acid, **CDDO**-Me (M. Sporn, AACR 2000, abstract180) on cell growth and apoptosis in leukemic cell lines and in primary AML. **CDDO**-Me decreased viability and induced apoptosis in different leukemic cell lines tested, with IC50 0.4, 0.4 and 0.3 muM in HL-60, KG-1 and NB4 cells respectively at 48 hrs. We observed decrease of mitochondrial membrane potential increase in annexin V binding and caspase-3 cleavage in ***CDDO*** -Me-treated cells suggesting induction of apoptosis as the primary mechanism of growth arrest. **CDDO**-Me did not affect Bcl-2 expression but induced Bax prior to caspase activation (by Northern blot analysis, ***CDDO*** -Me treatment induced Bax mRNA in both HL-60 and U937 cells, hence ***CDDO*** -Me may affect transcriptional regulation of Bax). HL-60-Dox cells with high expression of the MDR-1 gene were sensitive to **CDDO** -Me-induced killing, and blockade of MDR-1 by PSC-833 did not affect ***CDDO*** -Me cytotoxicity. In primary AML, **CDDO**-Me induced apoptotic cell death: 43.2% +- 5.2% at 0.5 muM (**CDDO**-Me - DMSO, n=4, 48hrs). **CDDO**-Me was a potent inducer of granulo-monocytic differentiation in HL-60 cells, with 86.6% of cells CD11b(+) at 0.1 muM, and induced monocytic differentiation in 2/5 AML. Colony formation of AML progenitors was significantly inhibited in a dose-dependent fashion, with 8.8% +- 3.8% surviving colonies at 0.5 muM (n=5). In contrast, colony formation of normal progenitors (n=3) was less inhibited (63% CFU-GM at 0.5 muM). ***CDDO*** -Me combined with ATRA **synergistically** decreased cell viability in leukemic cell lines and in 3/8 primary AML. In conclusion, ***CDDO*** -Me is an Mdr-1-independent compound that exerts strong antiproliferative, apoptotic and differentiating effects in myeloid leukemic cell lines and in primary AML samples in sub-micromolar concentrations. ***CDDO*** -Me-induced differentiation and growth inhibition is profoundly increased by combination with retinoids. Differential effects on leukemic and normal progenitor cells suggest potential efficacy of **CDDO**-Me in the treatment of hematologic malignancies.

CONCEPT CODE: Biochemistry studies - Proteins, peptides and amino acids 10064
General biology - Symposia, transactions and proceedings

(Hominidae)

L116 ANSWER 46 OF 49 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:299393 BIOSIS
DOCUMENT NUMBER: PREV200100299393
TITLE: The synthetic triterpenoid **CDDO**-Me is an effective inhibitor of the leukemia-associated de novo angiogenesis.
AUTHOR(S): Veiga, J. Pedro [Reprint author]; Nunes, Raquel [Reprint author]; Konopleva, Marina; Sallan, Stephen E. [Reprint author]; Sporn, Michael B.; Nadler, Lee M. [Reprint author]; Andreeff, Michael; Cardoso, Angelo A. [Reprint author]
CORPORATE SOURCE: Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 120a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Jun 2001
Last Updated on STN: 19 Feb 2002
ABSTRACT:Increasing evidence supports the hypothesis that acute lymphoblastic leukemia (ALL) cells and their bone marrow (BM) microenvironment collaborate for tumor cell growth and leukemia development. Specifically, we have shown that ALL cells secrete angiogenic factors that promote BM endothelial cell growth and reorganization and, conversely, that BM endothelium promotes the survival of leukemia cells. Therefore, one therapeutic strategy to target ALL would be to disrupt the privileged **interactions** between ALL and the BM endothelium. In an effort to identify such agents, we have studied the synthetic triterpenoids **CDDO** and **CDDO**-Me. These agents are ligands of PPAR-gamma, a transcription factor that we have previously identified as a potential target for anti-angiogenesis intervention in ALL. Using the Matrigel system, we observed that both **CDDO** and ***CDDO*** -Me inhibit the in vitro organization of BM endothelium into capillary-like structures, in a dose-dependent manner. Complete inhibition of BM endothelium from both ALL patients and normal donors was observed at 1muM of ***CDDO*** and 0.3muM of **CDDO**-Me. Of note, the inhibitory effects of the triterpenoids were not mediated by induction of apoptosis of BM endothelium since at time points at which endothelial networks were abrogated (24hrs), no significant inhibition was observed of endothelial cell survival or proliferation (100% survival at 1muM of **CDDO** and 83% survival at 0.3muM of **CDDO**-Me). Apoptosis of BM endothelium was observed at later time points (48 and 72hrs). Importantly, ALL BM plasma protects the BM endothelium from the inhibitory effects of these agents, requiring doses at least 10-fold higher. The efficacy of these triterpenoids in preventing the leukemia-promoted de novo angiogenesis was assessed in a murinoangiogenesis assay. In all cases tested (n= 8 patients), **CDDO**-Me (0.5muM), but not **CDDO** (1muM), prevented the angiogenic invasion of the implanted Matrigel promoted by the ALL BM plasma. In conclusion, we have demonstrated that the triterpenoid **CDDO**-Me abrogates the de novo angiogenesis promoted by ALL and, by disrupting the ALL: BM endothelium **interactions** may be a useful agent for the treatment of this disease.
CONCEPT CODE: Neoplasms - Blood and reticuloendothelial neoplasms 24010
General biology - Symposia, transactions and proceedings 00520
Pathology - Therapy 12512

00520
Cytology - Animal 02506
Cytology - Human 02508
Genetics - Human 03508
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Blood - Blood and lymph studies 15002
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Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508

INDEX TERMS: Major Concepts
Pharmacology; Blood and Lymphatics (Transport and Circulation); Tumor Biology

INDEX TERMS: Parts, Structures, & Systems of Organisms
granulocyte: blood and lymphatics, immune system; mitochondrial membrane; monocyte: blood and lymphatics, immune system

INDEX TERMS: Diseases
AML: blood and lymphatic disease, neoplastic disease, acute myeloid leukemia
Leukemia, Myeloid (MeSH)

INDEX TERMS: Chemicals & Biochemicals
ATRA [all-trans retinoic acid]: antineoplastic-drug; Bax; Bcl-2; **CDDO**-me [2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid-methyl ester]: antineoplastic-drug, antiproliferative, cytotoxicity, differentiating agent, proapoptotic, triterpenoid; MDR-1 [multidrug resistance 1]; PSC-833; annexin V; caspase-3; mRNA [messenger RNA]

INDEX TERMS: Methods & Equipment
Northern blot analysis: analytical method

INDEX TERMS: Miscellaneous Descriptors
apoptosis; growth arrest; progenitor colony formation; Meeting Abstract; Meeting Poster

ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
HL-60 cell line: human leukemia cells
HL-60-Dox cell line: human leukemia cells
KG-1 cell line: human acute myelogenous leukemia cells
NB4 cell line: human leukemia cells
U937 cell line: human promyelocytic leukemia cells
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

REGISTRY NUMBER: 121584-18-7 (PSC-833)
169592-56-7 (caspase-3)
302-79-4 (ALL-TRANS RETINOIC ACID)

GENE NAME: human MDR-1 gene [human multidrug resistance gene 1]

Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Immunology 24003
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508

INDEX TERMS: Major Concepts
Pharmacology; Blood and Lymphatics (Transport and Circulation); Tumor Biology

INDEX TERMS: Parts, Structures, & Systems of Organisms
bone marrow endothelium: blood and lymphatics, immune system; plasma: blood and lymphatics

INDEX TERMS: Diseases
acute lymphoblastic leukemia: blood and lymphatic disease, neoplastic disease, ALL
Leukemia, Lymphocytic, Acute (MeSH)

INDEX TERMS: Chemicals & Biochemicals
CDDO [2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid]: antineoplastic-drug, triterpenoid; **CDDO** -Me [2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid-methyl]: antineoplastic-drug, triterpenoid; Matrigel; PPAR-gamma [peroxisome proliferator-activated receptor gamma]

INDEX TERMS: Methods & Equipment
murine angiogenesis assay: analytical method

INDEX TERMS: Miscellaneous Descriptors
angiogenesis; apoptosis; Meeting Abstract; Meeting Poster

ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human: patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGANISM: Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

REGISTRY NUMBER: 119978-18-6 (Matrigel)

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ACCESSION NUMBER: 2002:8475 DISSABS Order Number: AAI3015490

TITLE: Differentiating and anti-inflammatory activities of the triterpenoid, **CDDO**: **Interactions** with transcription factors PPARgamma and NF-kappaB

AUTHOR: Wang, Yongping [Ph.D.]; Sporn, Michael B. [adviser]

CORPORATE SOURCE: Dartmouth College (0059)

SOURCE: Dissertation Abstracts International, (2001) Vol. 62, No. 5B, p. 2276. Order No.: AAI3015490. 152 pages.
ISBN: 0-493-25868-X.
DOCUMENT TYPE: Dissertation
FILE SEGMENT: DAI
LANGUAGE: English

ABSTRACT: A novel synthetic triterpenoid, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (**CDDO**), previously reported to have potent differentiating, anti-proliferative, and anti-inflammatory activities, has been identified as a ligand for the peroxisome proliferator-activated receptor .gamma. (PPAR.gamma.). **CDDO** induces adipocytic differentiation in 3T3-L1 cells, and binds to PPAR.gamma. with a Ki between 10-8 to 10-7 M. This binding is possible only in the absence of dithiothreitol (DTT). In transactivation assays, **CDDO** is a partial agonist for PPAR.gamma.. The methyl ester of **CDDO**, **CDDO**-Me, binds to PPAR.gamma. with similar affinity, but is an antagonist. Like other PPAR.gamma. ligands, **CDDO** **synergizes** with a retinoid X receptor (RXR)-specific ligand to induce 3T3-L1 differentiation, while **CDDO**-Me is an antagonist in this assay. The partial agonism of **CDDO** and the antagonism of **CDDO**-Me reflect the differences in their capacity to recruit or displace cofactors of transcriptional regulation; **CDDO** and rosiglitazone both release the nuclear receptor corepressor, NCoR, from PPAR.gamma., while **CDDO**-Me does not. The differences between **CDDO** and rosiglitazone as either partial or full agonists, respectively, are seen in the weaker ability of **CDDO** to recruit the coactivator CREB-binding protein, CBP, to PPAR.gamma..

In addition to the ability to induce adipocytic differentiation, **CDDO** also inhibits the induction of cyclooxygenase-2 (COX-2) in a colon fibroblast cell line (18Co) under the stimulation of interleukin 1.beta. (IL-1.beta.). COX-2 induction in this system is mediated by the activation of nuclear factor .kappa.B NF-.kappa.B and **CDDO** inhibits this activation by inhibiting the action of I-.kappa.B kinase (IKK). The inhibition of IKK leads to decreased phosphorylation and degradation of the inhibitor of NF-.kappa.B (I-.kappa.B), decreased activation of NF-.kappa.B and inhibition of COX-2 induction. In contrast, the induction of COX-2 by 12-O-tetradecanoylphorbol 13-acetate (TPA) in 18Co cells does not involve the activation of NF-.kappa.B and is not inhibited by **CDDO**. The inhibition of IKK in vitro is also sensitive to the presence of DTT, similar to the binding studies of **CDDO** and PPAR.gamma..

The role of DTT in the **interactions** between **CDDO** and its intracellular targets is examined by spectrophotometric methods. These studies demonstrate a reversible **interaction** between **CDDO** and DTT, as well as other thiol-containing compounds. In addition to **CDDO**, two structurally related triterpenoids, TP-139 and TP-82, and a PPAR.gamma. ligand of the prostaglandin family are used as electrophiles to study their **interactions** with different nucleophilic compounds containing hydroxyl, sulfhydryl and amino groups. The results confirm that **CDDO** is a highly active compound capable of **interacting**

with different nucleophiles, thus providing a molecular basis for its **interactions** with different intracellular targets.
CLASSIFICATION: 0419 HEALTH SCIENCES, PHARMACOLOGY

L116 ANSWER 48 OF 49 TOXCENTER COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:176808 TOXCENTER
COPYRIGHT: Copyright 2004 ACS
DOCUMENT NUMBER: CA13708109396G
TITLE: A novel dicyanotriterpenoid, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile, active at picomolar concentrations for inhibition of nitric oxide production
AUTHOR(S): Honda, Tadashi; Honda, Yukiko; Favaloro, Frank G.; Gribble, Gordon W.; Suh, Nanjoo; Place, Andrew E.; Rendi, Mara H.; Sporn, Michael B.
CORPORATE SOURCE: Department of Chemistry, Dartmouth College, Hanover, NH, 03755, USA.
SOURCE: Bioorganic & Medicinal Chemistry Letters, (2002) Vol. 12, No. 7, pp. 1027-1030.
CODEN: BMCLE8. ISSN: 0960-894X.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Journal
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2002:211223
LANGUAGE: English
ENTRY DATE: Entered STN: 20020813
Last Updated on STN: 20021224

ABSTRACT:
New oleanane triterpenoids with various substituents at the C-17 position of 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) and Me 2-carboxy-3,12-dioxooleana-1,9(11)-dien-28-oate were synthesized. Among them, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-onitrile shows extremely high inhibitory activity (IC50 = 1 pM level) against prodn. of nitric oxide induced by interferon-.gamma. in mouse macrophages. This potency is about 100 times and 30 times more potent than CDDO and dexamethasone, resp.
CLASSIFICATION CODE: 30-30
SUPPLEMENTARY TERMS: Miscellaneous Descriptors
triterpenoid oleanane prepn inhibitor nitric oxide macrophage; relationship structure activity dicyanotriterpenoid nitric oxide prodn; dioxooleanadienonitrile cyano antiinflammatory multifunctional prepn
REGISTRY NUMBER: 10102-43-9 (Nitric oxide)
508-02-1 (Oleanolic acid)
62-53-3 (Phenylamine)
100-46-9 (Benzylamine)
106-95-6 (Allyl bromide)
107-10-8 (Propylamine)
109-65-9 (Butyl bromide)
111-26-2 (Hexylamine)
111-83-1 (Octyl bromide)
288-13-1 (Pyrazole)
4897-50-1 (1,4'-Bipiperidine)
7051-34-5 (Cyclopropylmethyl bromide)
REGISTRY NUMBER: **218600-44-3**; 443103-07-9; 443103-21-7;
218600-53-4; 259525-93-4; 443102-65-6;
443102-70-3; 443102-75-8; 443102-80-5; 443102-85-0;
443102-90-7; 443102-94-1; 443102-97-4; 443103-02-4;
443103-14-8; 443103-28-4; 443103-35-3; 443103-41-1;
443103-47-7; 443103-53-5; 443103-59-1; 443103-65-9;
443103-71-7; 443103-77-3; 443103-83-1; 443103-89-7;
443103-95-5; 443104-02-7; 443104-08-3; 572-09-8;

218600-50-1; 443104-14-1; 443104-23-2; 443104-28-7;
443104-34-5; 443104-41-4; 443104-48-1; 443104-55-0

L116 ANSWER 49 OF 49 TOXCENTER COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:189365 TOXCENTER
COPYRIGHT: Copyright 2004 ACS
DOCUMENT NUMBER: CA13325350364N
TITLE: Synthetic Oleanane and Ursane Triterpenoids with Modified Rings A and C: A Series of Highly Active Inhibitors of Nitric Oxide Production in Mouse Macrophages
AUTHOR(S): Honda, Tadashi; Rounds, BarbieAnn V.; Bore, Lothar; Finlay, Heather J.; Favaloro, Frank G. ,Jr.; Suh, Nanjoo; Wang, Yongping; Sporn, Michael B.; Gribble, Gordon W.
CORPORATE SOURCE: Department of Chemistry, Dartmouth College Dartmouth Medical School, Hanover, NH, 03755, USA.
SOURCE: Journal of Medicinal Chemistry, (2000) Vol. 43, No. 22, pp. 4233-4246.
CODEN: JMCMAR. ISSN: 0022-2623.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Journal
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2000:632697
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20020403

ABSTRACT:
New olean- and urs-1-en-3-one triterpenoids with various modified rings C have been synthesized as potential antiinflammatory and cancer chemopreventive agents and evaluated for their inhibitory activities against prodn. of nitric oxide induced by interferon-.gamma. in mouse macrophages. These studies revealed that 9(11)-en-12-one and 12-en-11-one functionalities in ring C increase the potency by about 2-10 times compared with the original 12-ene. Subsequently, novel olean- and urs-1-en-3-one derivs. with nitrile and carboxyl groups at C-2 in ring A and with 9(11)-en-12-one and 12-en-11-one functionalities in ring C were synthesized. Among them, Me 2-cyano-3, 12-dioxooleana-1,9(11)-dien-28-oate, 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) (I), and Me 2-carboxy-3,12-dioxooleana-1,9(11)-dien-28-oate were found to have extremely high potency (IC50 = 0.1 nM level). Their potency is similar to that of dexamethasone although they do not act through the glucocorticoid receptor. Overall, the combination of modified rings A and C increases the potency by about 10 000 times compared with the lead compd., 3-oxooleana-1,12-dien-28-oic acid (IC50 = 1 .mu.M level). The selected oleanane triterpenoid, I, was found to be a potent, multifunctional agent in various in vitro assays and to show antiinflammatory activity against thioglycollate-interferon-.gamma.-induced mouse peritonitis.

CLASSIFICATION CODE: 30-30
SUPPLEMENTARY TERMS: Miscellaneous Descriptors
triterpenoid oleanane ursane prepn inhibitor nitric oxide macrophage; dioxooleanadienoic cyano acid antiinflammatory multifunctional prepn; relationship structure activity triterpenoid oleanane ursane nitric oxide prodn
REGISTRY NUMBER: 77-52-1 (Ursolic acid)
508-02-1 (Oleanolic acid)
4861-79-4 (Methoxymagnesium methyl carbonate)
5470-11-1 (Hydroxylamine hydrochloride)
REGISTRY NUMBER: 69660-90-8; 151071-49-7; 194235-18-2; 218600-46-5; 259526-01-7; 259526-02-8; 259526-03-9; 259526-04-0; 259526-05-1; 259526-06-2; 259526-07-3; 272107-83-2; 272107-84-3; 194235-23-9; 194235-30-8; **218600-53-4** ; 259525-93-4; 259526-10-8; 259526-13-1; 259526-14-2; 305818-25-1; 305818-26-2; 305818-27-3; 305818-28-4; 305818-29-5; 305818-30-8; 305818-32-0; 194235-17-1;

194235-25-1; 194235-27-3; 194235-33-1; 194235-35-3;
194235-37-5; 194238-80-7; **218600-44-3**;
252850-56-9; 259526-11-9; 259526-15-3; 305818-31-9;
305818-33-1; 305818-34-2; 305818-35-3; 13720-16-6;
22425-72-5; 25493-94-1; 65023-20-3; 74799-45-4;
194235-42-2; 197500-53-1; 65023-19-0; 108776-85-8;
112899-58-8; 120638-95-1; 132915-43-6; 218600-50-1;
218600-52-3; 222419-55-8; 259526-08-4; 259526-12-0;
305818-36-4; 305818-37-5; 305818-39-7; 305818-40-0;
305818-41-1; 305818-42-2; 305818-43-3; 305818-44-4;
305818-45-5; 305818-46-6

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